

Interventions to Improve Adherence to Antiretroviral Therapy:

A Review of the Evidence

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ACRONYMS

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
DAART	Directly Administered Antiretroviral Therapy
DOT	Directly Observed Treatment
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
ICIUM	International Conference on Improving Use of Medicines [WHO]
IDUs	injection drug users
M-DAART	Modified DAART
M-DOT	Modified DOT
MEMS	Medication Event Monitoring System
MeSH	Medical Subject Headings
MI	motivational interviewing
OI	opportunistic infection
PI	protease inhibitor
PLWHA	people living with HIV/AIDS
PMTCT	prevention of mother-to-child transmission
RCT	randomized controlled trial
RNA	ribonucleic acid
RPM Plus	Rational Pharmaceutical Management Plus Program
TB	tuberculosis
USD	U.S. dollar
VCT	voluntary counseling and testing

INTRODUCTION

The advent of antiretroviral (ARV) medicines in developed countries in the mid-1990s radically transformed human immunodeficiency virus (HIV) infection from a fatal illness to a more manageable disease, thereby greatly improving the lives of people living with HIV/AIDS (PLWHA). Nevertheless, for a number of reasons, such as high medicine prices and lack of political motivation at national and international levels, advances made in treating the virus that causes acquired immunodeficiency syndrome (AIDS) have taken a long time to translate into a reality for the majority of HIV patients in resource-constrained settings. Only now, a decade later, some of those barriers are being overcome, and access to affordable antiretroviral therapy (ART) is slowly becoming more widely available.

The need to address the HIV epidemic in resource-constrained settings, through a combination of treatment and prevention efforts, could not be more urgent. The impact of the epidemic is widespread at every level of society—spanning the household, agriculture, education, and health sectors. The impressive economic and social development achievements accomplished over previous decades are rapidly eroding as a result of widespread HIV infection, which in turn causes problems that include reduced or total loss of income due to illness affecting one or more family member, fewer crops planted or harvested because farm workers are too ill to work, compromised quality of instruction due to reduced number or lack of teachers, and fewer children enrolled in schools because of financial burden. In the health sector, existing personnel are overwhelmed because of the rising number of PLWHA who need health care, while families and individuals bear the burden of suffering and death.

With increased availability and affordability of ART in poorer settings, the urgent questions concern—

- Case finding: how to most effectively reach potentially HIV-positive individuals who often do not know or do not want to know their serostatus to provide them with voluntary counseling and testing (VCT).
- Service provision: how to ensure that HIV-positive individuals, especially mothers, access and use prevention of mother-to-child transmission (PMTCT), PMTCT Plus, or ART.
- Case holding: how to ensure that adherence barriers for HIV-positive individuals who begin long-term ART are minimized.

In each society or culture, the population's knowledge, understanding, and attitudes toward HIV and AIDS must be taken into consideration to help understand the factors inhibiting uptake of VCT, PMTCT, and ART services and therapy and to identify locally appropriate effective interventions to answer these questions and overcome these barriers.

Available evidence from resource-constrained settings on interventions being used in developed and developing countries is presented in this paper with the goal of better understanding how to

improve adherence to ART. Although evidence is available from both high-income settings and resource-constrained settings on existing common barriers in accessing and adhering to ART, it is unclear what interventions, if any, are being used to overcome those barriers in resource-constrained settings. This paper is written with a view to the future, aiming to capture what evidence exists from both settings and to discuss possible implications of lessons learned from high-income settings for HIV/AIDS programs in resource-constrained settings.

The following background section provides a brief history of ARV rollout in resource-constrained settings, gives a short overview of common factors inhibiting access to and use of HIV/AIDS services, and offers background to key ART adherence issues. The next section describes the methodology and findings from a literature review that aimed to capture developed and developing-country experience with interventions to improve adherence to ART. Next is a discussion section outlining key findings and recommendations for future research. The paper closes with a brief conclusion.

BACKGROUND

ART Provision in Resource-Constrained Settings

Provision of ART in resource-constrained countries settings faced a number of challenges, one of which not surprisingly was cost. In 2000, the cost of ART per patient per year was approximately 10,000 to 12,000 U.S. dollars (USD),¹ a cost well beyond the reach of almost all patients in resource-constrained settings. In addition to the expenditure for ART, patients often were and often still are responsible for the expense of managing side effects and other opportunistic infections (OIs), as well as for the costs of laboratory tests (HIV-positive testing, ribonucleic acid [RNA] viral load, CD4+, etc.). Despite the daunting concern of cost, several countries in Latin America (Brazil, Costa Rica) and the Caribbean (St. Kitts, Barbados, and Grenada) proclaimed and demonstrated full political commitment to universal provision of free ART to their HIV-positive populations.² As a result, by the end of 2001, about 170,000 people in those regions were receiving free ARVs.³ A few other countries have since followed suit: for example, Botswana initiated efforts to institute universal provision of ARVs in 2002.⁴ More recently, several global initiatives undertaken by nongovernmental organizations, private foundations, governments, the pharmaceutical industry, or some combination thereof⁵ have helped reduce the price of ART and increase the number of patients in low-income settings who are able to access treatment. While cost remains one of the major barriers in the uptake of ART services,⁶ evidence clearly indicates that it is becoming less of a barrier to accessing ART.

Additional potential constraints to providing ART in resource-constrained settings include poor or inadequate health care and laboratory infrastructure, insufficient numbers of well-trained personnel, and administrative hurdles.⁷ Although those concerns are often legitimate, the increasing availability of ARVs in recent years has shifted the focus of concern from poor or lacking infrastructure as a barrier to ART provision. Currently, an urgent need exists to determine how best to rapidly scale up physical and human resources to cope with the increased availability of ART and how best to take advantage of already existing resources to assist in that process.

¹ Joint United Nations Programme on HIV/AIDS (UNAIDS). *Report on the Global HIV/AIDS Epidemic* (Geneva: UNAIDS, 2002).

² P. Chequer, P. Cuchi, R. Mazin, et al. Access to Antiretroviral Treatment in Latin American Countries and the Caribbean, *AIDS* 16, Suppl. no. 3 (2002): S50–S57.

³ Ibid.

⁴ Jude Nwokike, personal communication, 2004.

⁵ Recent initiatives, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria or the President's Emergency Plan for AIDS Relief, Médecins Sans Frontières Campaign for Access to Essential Medicines, and the Clinton Foundation, further support this argument.

⁶ Editorial. Adherence to Antiretroviral Treatment in Africa: Cost is the Main Obstacle, *Prescrire International* 13, no. 72 (August 2004): 151–52. Translated from *La Revue Prescrire* 24, no. 250 (May 2004): 379–80.

⁷ R. S. Hogg, A. E. Weber, K. J. P. Craib, et al. One World, One Hope: The Cost of Providing Antiretroviral Therapy to All Nations, *AIDS* 12 (1998): 2203–9.

ART introduction has not only increased significantly over the last few years, but recent evidence from resource-constrained settings has also revealed that provision of ART in these settings, while often challenging, is possible.^{8,9,10,11}

Barriers That Inhibit Individuals Coming Forward for VCT

Recent estimates indicate that at least 90 percent of HIV-positive individuals in the developing world are not aware of their serostatus.¹² One of the most significant factors that discourages people from taking an HIV test is the fear of the possible consequences of receiving a positive result—stigma and discrimination. This real issue is highlighted by Day and colleagues in a survey conducted in South Africa that revealed that only 14 percent of respondents would access testing services given the “potential consequences [of testing positive] such as stigma, death and disease,”¹³ even if treatment for HIV was available. People living with HIV have historically been discriminated against, irrespective of the setting (high-income or resource-constrained). One noteworthy example of discrimination was reported in South Africa where, during the early stages of the AIDS crisis, a woman was killed by her fellow villagers when she disclosed her HIV status.¹⁴ In some cases, AIDS-related stigma and discrimination hinders the effectiveness of the response to the epidemic by increasing transmission of the virus from mothers to newborns if HIV-positive mothers continue to breastfeed their children for fear of the repercussions of disclosure of their serostatus.¹⁵

The Problem of Adherence in the Developing and Developed World

Is adherence a problem on a lesser, greater, or similar scale in developing countries than in the developed world? The simple answer is that it is probably too soon to say. Evidence from studies in a few resource-constrained countries (Senegal,¹⁶ South Africa,¹⁷ Haiti,¹⁸ and Uganda^{19,20})

⁸ L. G. Bekker, C. Orrell, L. Reader, et al. Antiretroviral Therapy in a Community Clinic: Early Lessons from a Pilot Project, *South African Medical Journal* 93, no. 6 (2003): 458–62.

⁹ P. Farmer, F. Leandre, J. S. Mukherjee, et al. Community-Based Approaches to HIV Treatment in Resource-Poor Settings, *The Lancet* 358 (2001): 404–9.

¹⁰ C. Laurent, N. Diakhate, Ndeye Fatou Ngom Gueye, et al. The Senegalese Government HAART Initiative: An 18 Month Follow-up Study, *AIDS* 16 (2002): 1363–70.

¹¹ D. Coetzee, A. Boule, K. Hildebrand, et al. Outcomes at 24 Months in a Primary Care Antiretroviral Treatment Programme in South Africa, *AIDS* 18 (2004): 1–9.

¹² UNAIDS. *Report on the Global AIDS Epidemic: 4th Global Report* (Geneva: UNAIDS, 2004).

¹³ J. H. Day, K. Miyamura, A. D. Grant, et al. Attitudes to HIV Voluntary Counseling and Testing among Mineworkers in South Africa: Will Availability of Antiretroviral Therapy Encourage Testing? *AIDS Care* 15, no. 5 (2003): 665–72.

¹⁴ Associated Press. HIV Positive S. African Woman Murdered, <<http://www.aegis.com/news/ap/1998/AP981219.html>> Dec. 28, 1998 (accessed Aug. 18, 2004).

¹⁵ See note 12.

¹⁶ See note 10.

¹⁷ C. Orrell, D. R. Bangsberg, M. Badri, et al. Adherence Is Not a Barrier to Successful ART in South Africa, *AIDS* 17 (2003): 1369–75.

¹⁸ T. Kasper, D. Coetzee, F. Louis, et al. Demystifying Antiretroviral Therapy in Resource-Poor Settings, *Essential Drugs Monitor Issue* 32 (2003): 20–21.

shows that high levels of adherence—often higher than in developed countries—can be achieved, even where patients must pay for medicines. Some of those studies, however, have been criticized for having “relatively strict exclusion criteria...and study populations tend to be urban with above average education and income, which is not generally representative of most African patients requiring treatment.”²¹ Evidence of less than optimal levels of adherence from resource-constrained settings also exists.²²

The extent to which ART adherence is presently or may become a problem in resource-constrained settings is unclear. ARVs must be taken for a patient’s lifetime, and high levels of adherence are required to maintain the functionality of the individual’s immune system and to slow the emergence of resistant strains. Therefore, in both individual and public health terms, HIV/AIDS treatment programs should measure and monitor adherence levels and seek to identify ART clients with difficulties in adhering to treatment as early as possible.

Adherence and Slowing the Development of ART-Resistant Strains of the Virus

One key challenge to ART is the commitment and ability of HIV-positive individuals to adhere to long-term therapy. Adherence to ART has been defined as “the ability of the person living with HIV/AIDS to be involved in choosing, starting, managing and maintaining a given therapeutic combination medication regimen to control viral (HIV) replication and improve immune function.”²³ Failure to adhere to the proper treatment protocols results in individual treatment failure (inability to keep RNA viral load low and inability to increase CD4+ levels and subsequent deterioration of the immune system) and can also lead to development of resistant strains of the virus.

ART resistance has been reported in many recent studies of newly infected HIV-positive patients.^{24,25} In Europe and North America, more than half of all patients on ART show signs of

¹⁹ J. Oyugi, J. B. Byakika-Tusiime, E. Charlebois, et al. Multiple Validated Measures of Adherence Indicate High Levels of Adherence to Generic HIV Antiretroviral Therapy in Resource-limited Settings, *JAIDS* 36, no. 5 (2004): 1100–1102.

²⁰ J. H. Oyugi, J. T. Byakika, K. Ragland, et al. *Treatment Outcomes and Adherence to Generic Triomune® and Maxivir® Therapy in Kampala, Uganda*, Abstract WeOrB1323, XV International AIDS Conference (July 11–16, 2004), Bangkok (and personal communication, 2004).

²¹ W. Stevens, S. Kaye, and T. Corrah. Antiretroviral Therapy in Africa, *British Medical Journal* 328, no. 7434 (2004): 280–282.

²² M. R. Kamya, L. A. Spacek, H. M. Shihab, et al. *Treatment Outcomes for Antiretroviral Therapy in a Routine Clinical Setting in Kampala, Uganda*, Abstract PL4.4, 7th International Congress on Drug Therapy in HIV Infection (November 14–18, 2004), Glasgow.

²³ A. A. Jani, ed. *Adherence to HIV Treatment Regimens: Recommendations for Best Practices* (Washington, DC: American Public Health Association [APHA], 2002), http://www.apha.org/ppp/hiv/Best_Practices.pdf (accessed Feb. 27, 2006).

²⁴ H. Salomon, M. A. Wainberg, B. Brenner, et al. Prevalence of HIV-1 Resistant to Antiretroviral in 81 Individuals Newly Infected by Sexual Contact or Injecting Drug Use, *AIDS* 14, no. 2 (2000): F17–F23.

²⁵ D. Boden, A. Hurley, L. Zhang, et al. HIV-1 Drug Resistance in Newly Infected Individuals, *JAMA* 282 (1999): 1135–49.

drug resistance.²⁶ This finding may be because many of those patients were primarily exposed to ARV monotherapy to treat HIV—which has been shown to lead to a more rapid development of resistance than use of combination medications—before combination ART therapy became widely understood and available.

Some have argued that in developing countries, where the majority of patients are treatment-naïve, the likelihood of widespread resistance emerging is considerably less.²⁷ Others argue that resistance is as significant an issue in less-developed countries as in developed ones. Recent reports from China, which recently began rolling out ART,²⁸ indicate that HIV/AIDS patients receiving ARV medications free of charge have already begun to develop resistance.²⁹ In addition, recent reports³⁰ indicate resistance among treatment-naïve HIV-positive individuals in high-income countries, and other reports exist of resistance in resource-constrained settings in Uganda (mainly caused by nonadherence due to high ART cost).³¹

Regardless of the extent to which resistance or the reason for its development may differ between the two settings, clearly, better adherence reduces the opportunity for developing resistance while maintaining the patient in more stable health.

Lack of “Gold Standard” for Measuring Adherence

Physicians differ in their definitions of what is considered optimum adherence—adherence may mean taking pills regularly at specified times, or it may mean taking into consideration the dietary restrictions that are specified for certain medications. Whatever the case, the optimum level of adherence for treatment of HIV using ARV medicines is still not clear, even in developed countries where ART has been around for a decade. Most of the studies reviewed for this paper use a variety of adherence levels: certain programs and researchers use an adherence standard of 80 percent^{32,33} of doses (which is the target commonly used for other diseases, such as tuberculosis, hypertension, or diabetes, when treatment is short term); most studies recommend ≥ 95 percent,³⁴ and some even aim for a perfect 100 percent of doses.³⁵

²⁶ J. M. A. Lange, J. Perriens, D. Kuritzkes, et al. What Policymakers Should Know about Drug Resistance and Adherence in the Context of Scaling-up Treatment of HIV Infection, *AIDS* 18, Suppl. no. 3 (2004): S69–S74.

²⁷ Ibid.

²⁸ China received a grant from GFATM in August 2004 to fund its community-based HIV treatment program. See http://www.kaisernetwork.org/daily_reports/rep_index.cfm?hint=1&DR_ID=25348 for additional information.

²⁹ Kaiser Family Foundation. HIV Patients in China’s Free Antiretroviral Distribution Program Developing Resistance to Drugs, *Kaiser Family Foundation Daily HIV/AIDS Report* (Dec. 6, 2004), <http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=27074> (accessed Dec. 17, 2004).

³⁰ L. Ross, et al. *Prevalence of Antiretroviral Drug Resistance and Resistance Mutations in Antiretroviral Therapy (ART)-Naïve HIV-Infected Individuals from 40 US Cities during 2003*, Abstract H-173, 44th Interscience Conference on Antimicrobial Agents and Chemotherapy (October 30–November 2, 2004), Washington, DC.

³¹ See note 23.

³² C. Laine, C. J. Newschaffer, D. Zhang, et al. Adherence to Antiretroviral Therapy by Pregnant Women Infected with Human Immunodeficiency Virus: A Pharmacy Claims-Based Analysis, *Obstetrics and Gynecology* 95, no. 2 (2000): 167–73.

³³ See note 10.

³⁴ J. A. Bartlett. Addressing the Challenges of Adherence, *Journal of Acquired Immune Deficiency Syndrome* 29 (2002): S2–S10.

In addition, no consensus exists on the optimal method for measuring adherence; indeed experts are only unanimous in their agreement that no gold standard exists for measuring adherence. In the studies reviewed, researchers used several different measures (and often some combination thereof) to determine adherence levels, such as electronic devices, pill counts, directly observed treatment (DOT), and patient self-report. Table 1 provides a brief summary of the most common methods used to measure adherence as well as the corresponding perceived advantages and disadvantages of each method.

³⁵ A.J. Durante, C.A. Bova, K.P. Fennie, et al. Home-Based Study of Anti-HIV Drug Regimen Adherence among HIV-Infected Women: Feasibility and Preliminary Results, *AIDS Care* 15, no. 1 (2003): 103–15.

Table 1. Examples of Common Methods Used to Measure Adherence: Advantages and Disadvantages

Method	Brief Description	Rates Reportedly Achieved in Papers Reviewed	Advantages	Disadvantages
Self-report	<p>One of the most common methods to measure adherence, given its low cost.</p> <p>Patient reports the number of pills taken to provider, who records this rate against the patient's medical history. Various different forms exist, such as medication diaries, self-administered questionnaire, and patient-provider interviews.</p> <p>One self-report tool that has been used in several studies is the Adult AIDS Clinical Trial Group questionnaire developed by M. A. Chesney and colleagues,³⁶ which consists of two self-report questionnaires that assess adherence behavior as well as analyze patients' adherence to dosing requirements.</p>	<p>85%³⁷ 95%³⁸</p>	<p>Less expensive.</p> <p>Patient may feel that she or he has more hands-on involvement in health care decisions.</p>	<p>Patients may exaggerate the number of pills taken and general adherence behavior.</p>

³⁶ This is described in more detail in M. A. Chesney, J. R. Ickovics, D. B. Chambers, et al. Self-Reported Adherence to Antiretroviral Medications among Participants in HIV Clinical Trials: The AACTG Adherence Measurement Instruments, *AIDS Care* 12 (2000): 255–66.

³⁷ A. L. Gifford, J. E. Bormann, M. L. Shively, et al. *Effects of Group HIV Patient Education on Adherence to ARVs: A Randomized Controlled Trial*, Abstract 479, 8th Conference on Retroviruses and Opportunistic Infections (February 4–8, 2002), Chicago, IL.

³⁸ P. Blasco. *Improving Adherence to ART in Children in Resource-Limited Settings*, Abstract HI001, International Conference on Improving the Use of Medicines (ICIUM) (March 30–April 2, 2004), Chiang Mai, Thailand.

Method	Brief Description	Rates Reportedly Achieved in Papers Reviewed	Advantages	Disadvantages
Pill count	The number of pills that the patient is provided is counted at the start of treatment and intermittently as the weeks go by to ascertain whether the patient is taking the medication.	90% ³⁹	Less expensive.	<p>Patient may not actually be taking the pills and might even be throwing them away.</p> <p>Time-consuming: requires a nurse or health official from the provider clinic or health center to count the pills.</p> <p>Does not provide an accurate perspective of the patient's medication-taking behavior.</p>
Electronic devices	The patient is provided with an electronic device that records the timing of the medication-taking behavior. The most widely used appears to be the Medication Event Monitoring System (MEMS), ⁴⁰ which is an electronic device placed in the cover of the pill bottle that records each time the bottle is opened as a dosing event. Another example is the Disease Management Assistance System that, in addition to providing verbal reminders, also records dosing times.	70% ⁴¹ 95% ⁴²	Can be expensive.	<p>Expensive and not likely to be feasible in resource-constrained settings.</p> <p>In the case of MEMS, the possibility of receiving inaccurate readings exists because the pill bottle may be opened on occasions when the medication is not taken; however, MEMS will record this occurrence as a dosing event.</p>

³⁹ R. Broadhead, D. D. Heckathorn, F. L. Altice, et al. Increasing Drug Users' Adherence to HIV Treatment: Results of a Peer-driven Intervention Feasibility Study, *Social Science Medicine* 55, no. 2 (2002): 235–46.

⁴⁰ MEMS is developed by Aprex Corp and has been available since 1990.

⁴¹ S. A. Safren, E. S. Hendriksen, N. Desousa, et al. Use of an On-line Pager System to Increase Adherence to Antiretroviral Medications, *AIDS Care* 15, no. 6 (2003): 787–93.

⁴² A. Andrade, H. Davis, S. Celano, et al. *Intervention Trial Using a Novel Electronic Device in HAART Indicators: Impact of Cognitive Dysfunction*, Abstract 602, 8th Conference on Retroviruses and Opportunistic Infections (February 4–8, 2001), Chicago, IL.

Method	Brief Description	Rates Reportedly Achieved in Papers Reviewed	Advantages	Disadvantages
DOT	Although this strategy falls into the category of an intervention to improve adherence, DOT can also be a method for measuring adherence by itself. The patient is monitored while taking the medication by a health care worker or family member who is assigned to the patient for that purpose.	92% ⁴³	Effective means of measuring adherence because it is based on direct observation of the medication-taking event.	Less cost-effective and time consuming: requires the presence of another individual who might need to be paid for providing this service, and in cases where patients are not in a "captive" setting, the individual might need to travel to the patient's home or the setting where the medication event will occur.
Pharmacy record review	Health care provider reviews the patient's pharmacy records to determine levels of patient adherence. Doses are either by DOT and recorded accordingly, or certain quantities of ARVs are dispensed to each individual patient.	Not used in any papers reviewed.	Advantages of DOT, if doses given under DOT.	Can only be assured to be 100% correct when all doses are observed and properly recorded by health provider. If a certain quantity is dispensed, can only assume patient is consuming them and appropriately.

⁴³ B. Stephenson, D. Wohl, D. Rosen, et al. *Directly Observed Therapy (DOT) Does Not Ensure Adherence to Antiretroviral Therapy among HIV-infected Inmates*, Abstract 13143, American Public Health Association (APHA) Conference (November 12–16, 2000), Boston, MA.

As described in Table 1, each method used for measuring adherence has advantages and disadvantages that range from cost to reliability. None is optimal: for example, although two studies^{44,45} that compare the use of MEMS with self-report concluded that adherence levels were higher using self-report, overestimation by self-report patients could have been taking place.⁴⁶ Therefore, to improve accuracy researchers quite commonly use a combination of methods to measure adherence.

Factors That Impede ART Adherence in Developing- and Developed-Country Contexts

In addition to price and availability, several other factors exist that can impede the achievement of optimum adherence levels. A considerable amount of research has been done on those factors in developed and developing countries, categorized as follows—

- Regimen-related factors: such as pill burden or medication side effects
- Patient-related factors: such as the patient's own belief system, psychological and social issues, or the patient-provider relationship⁴⁷

Regimen-Related Factors

Regimen-related factors can pose significant barriers to optimum adherence. ART medication should be taken at specific times of the day, and if this requirement interferes with the set lifestyle of the patient, adherence could be greatly compromised. In addition, certain ARVs can be taken without meals (efavirenz, nevirapine, abacavir, stavudine, and zidovudine), whereas others need to be taken with meals (tenofovir) in order to work correctly.⁴⁸

Recent patient surveys point out that the more complex the regimen, the less the patient will accurately understand the dosing frequency.⁴⁹ A high pill burden (a high number of tablets/day) may result in poorer adherence; it has been reported that simpler HIV regimens with fewer pills

⁴⁴ J. H. Arnstein, P. A. Demas, H. Farzadegan, et al. Antiretroviral Therapy Adherence and Viral Suppression in HIV-Infected Drug Users: Comparison of Self-Report and Electronic Monitoring, *Clinical Infectious Diseases* 33 (2001): 1417–23.

⁴⁵ K. M. Melbourne, S. M. Geletko, S. L. Brown, et al. Medication Adherence in Patients with HIV Infection: A Comparison of Two Measurement Methods, *AIDS Reader* 9, no. 5 (1998): 329–38.

⁴⁶ Some, however, feel that it is well-established that self-reporting overestimates adherence (Paul Arnow, personal communication, February 1, 2005). However, this finding was not substantiated by evidence collected as part of this review.

⁴⁷ E. Sabaté, ed. Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome, in *Adherence to Long-Term Therapies: Evidence for Action* (Geneva: World Health Organization, 2003).

⁴⁸ T. Castleman, E. Seumo-Fosso, and B. Cogill. Food and Nutrition Implications of ART in Resource-Limited Settings, *FANTA Technical Note No. 7* (2003). <http://www.fantaproject.org/publications/tn7.shtml> (accessed May 2004).

⁴⁹ E. S. Daar, C. Cohen, R. Remien, et al. Improving Adherence to Antiretroviral Therapy, *AIDS Reader* 13, no. 2 (2003): 81–90.

can have a positive effect on adherence.⁵⁰ Pill taste, size, and shape can pose additional barriers to adherence.⁵¹ Not surprisingly, side effects, severe and less severe, can also greatly compromise adherence.⁵²

Patient-Related Factors

Patient-related factors can pose significant barriers to optimum ART adherence and may be more difficult to tackle than medication-related factors. The physician has less control over the patient's behavior, the decisions that the patient makes with regard to intake of medication, and the patient's perception of the need to take the medication and the resulting outcomes. As voiced by a recent World Health Organization report on adherence, "a patient's behavior is the critical link between a prescribed regimen and treatment outcomes."⁵³

Knowledge of and information about the importance of ART can figure prominently in patients' adherence decisions. For example, evidence indicates that patients adhere better who believe ART is effective and that not adhering properly to ART could lead to viral resistance.⁵⁴

Evidence exists that a patient's psychological issues can be likely inhibitors to adherence. For example, depression is a factor that has the potential to compromise treatment outcomes and adherence.⁵⁵ Considerable debate has occurred about the impact of patient-related factors such as alcohol and substance abuse on adherence. Selected evidence^{56,57,58} suggests that alcohol and substance abuse contribute to low rates of adherence, while other evidence⁵⁹ indicates that injection drug users (IDUs)—a group that can be more likely to adhere to therapy than others—is also a group that is less likely to initiate ART.

Social and demographic factors may play an important role in a patient's ability to adhere properly: demographic factors such as race, age, gender, and income level have been cited in developed countries as potential determinants of attaining good adherence.^{60,61,62} However, some

⁵⁰ V. E. Stone, J. Clarke, J. Lovell, et al. HIV/AIDS Patients' Perspectives on Adhering to Regimens Containing Protease Inhibitors, *Journal of General Internal Medicine* 13 (1998): 586–93.

⁵¹ D. A. Murphy, K. Johnston Roberts, D. Hoffman, et al. Barriers and Successful Strategies to Antiretroviral Adherence among HIV-Infected Monolingual Spanish-Speaking Patients, *AIDS Care* 15, no. 2 (2003): 217–30.

⁵² S. Duran, M. Saves, B. Spire, et al. Failure to Maintain Long-Term Adherence to Highly Active Antiretroviral Therapy: The Role of Lipodystrophy, *AIDS* 15 (2001): 2441–44.

⁵³ See note 50.

⁵⁴ N. Wenger, Gifford A, Liu H, et al. *Patient Characteristics and Attitudes Associated with (AR) Adherence*, Abstract 98, 6th Conference on Retroviruses and Opportunistic Infections (January 31–February 4, 1999), Chicago.

⁵⁵ International Conference for Improving the Use of Medicines (ICIUM) website, ICIUM 2004 Theme Summary: HIV/AIDS, <http://www.icium.org> (accessed November 2004).

⁵⁶ V. Gordillo, J. del Almo, V. Soriano, et al. Sociodemographic and Psychological Variables Influencing Adherence to Antiretroviral Therapy, *AIDS* 13 (1999): 1763–69.

⁵⁷ See note 37.

⁵⁸ See note 59.

⁵⁹ A. Mocroft, S. Madge, A. M. Johnson, et al. A Comparison of Exposure Groups in the EuroSIDA Study: Starting HAART, Response to HAART and Survival, *JAIDS* 22 (1999): 369–78.

⁶⁰ B. D. Adam, E. Maticka-Tyndale, and J. J. Cohen. Adherence Practices among People Living with HIV, *AIDS Care* 15, no. 2 (2003): 263–74.

⁶¹ I. Escobar, M. Campo, J. Martin, et al. Factors Affecting Patient Adherence to Highly Active Antiretroviral Therapy, *The Annals of Pharmacotherapy* 37 (2003): 775–81.

researchers⁶³ feel that these social and demographic factors do not play a significant role in adherence and could possibly be misleading for physicians who decide to use those factors as an indication of a patient's ability to adhere, especially given the fact that evidence⁶⁴ suggests providers are often poor predictors of good adherence.

Similar Factors Detrimental to Adherence in Developing and Developed Countries

Where ARVs are available and affordable, evidence from studies conducted in high-income settings has shown that factors that act as barriers to adherence appear to be quite similar to those barriers found in resource-constrained settings. In Cameroon, for example, the same set of regimen-related and patient-related issues reported in developed-country settings (such as pill burden or side effects) are simply magnified.⁶⁵ Common factors inhibiting adherence included patients' forgetting to take medications, difficulty in fitting medication schedules into daily routines, shame in getting refills, and level of conviction regarding the efficacy of the medication.

Overcoming the Barriers: What Are the Successes?

There is a consensus in the literature on what factors may inhibit successful adherence. However, the literature describing successful interventions, even those found in developed countries, to improve adherence is relatively weak. The research is almost nonexistent about successful interventions in resource-constrained settings, one indicator that ARV medicines are only now becoming more widely available.

In the following section, findings will be discussed from a literature review on the various forms of interventions used to improve treatment of HIV with ARV medicines by maintaining high levels of adherence.

⁶² See note 59.

⁶³ L. J. Eldred, A. W. Wu, R. E. Chaisson, et al. Adherence to Antiretroviral and Pneumocystis Prophylaxis in HIV Disease, *JAIDS* 18 (1998): 117–25.

⁶⁴ B. A. Boyle. Getting and Keeping Patients on HAART, *AIDS Reader* 9, no. 6 (1999): 378–80, 409.

⁶⁵ K. N. Muko, V. C. Ngwa, E. Tebo, et al. Adherence to HAART: A Self-Reported Case Study from a Rural Area in Cameroon. Copy of an unpublished paper shared personally with the authors.

LITERATURE REVIEW: EXPERIENCE WITH INTERVENTIONS TO IMPROVE ADHERENCE TO ART

Purpose

The literature review sought to capture developed- and developing-country experience with interventions to improve adherence and to identify how lessons from high-income settings can be applied in resource-constrained settings.

Methodology

In order to conduct the literature review, a comprehensive search of MEDLINE/PubMed was carried out using both Medical Subject Headings (MeSH) and non-MeSH terms related to ART, HIV, health behavior, behavior and behavior mechanisms, and patient acceptance of health care. (See Annex 1 for a list of the exact terms used.) The literature search, which was conducted between May and July 2004, was limited to articles published between 1995 and 2004.

In order to broaden the search and to capture nonpublished material, a request for information was also sent to the following e-mail discussion groups—

- E-drug e-mail discussion group: e-drug@usa.healthnet.org
- Procaare-ART e-mail discussion group: <http://www.procaare.org/subscribe.php>
- Several individuals working in global health (specifically HIV/AIDS) either known personally by the authors or recommended by colleagues

Although the initial aim was to include only scientifically rigorous papers in the literature review, less rigorous studies as well as studies where the methodology was unclear were also included. Inclusion of those studies allowed the authors to capture more experience with types of interventions being used, though it did not allow the authors to thoroughly evaluate the effectiveness of those interventions.

In addition, relevant abstracts were included in the review to capture more developing-country experience. Abstracts reviewed were acquired through references from articles identified by the literature search. The primary abstract database researched was that from the XV International Conference on HIV/AIDS (Bangkok 2004).⁶⁶ The literature review also included relevant articles recommended by colleagues but that were not captured by the rigorous review.

⁶⁶ eJournal of the International AIDS Society, Medscape, Complete Abstracts of the XV International AIDS Conference (Online), <http://www.iasociety.org/ejias-search/search.asp> (accessed Dec. 2004).

Findings: Interventions to Improve Adherence to ART

Although the literature on factors impeding ART adherence is extensive—for both high-income and resource-constrained settings—only in recent years has more literature surfaced on interventions to improve long-term adherence to HIV treatment. Published material is significantly lacking on the impact and cost-effectiveness of different interventions to improve ART adherence in either setting.

Profile of Papers

Using MEDLINE/PubMed, more than 200 articles were collected, of which 43 described interventions to improve adherence. Of those 43, 21 were abstracts—not full papers in peer-reviewed journals. Very few of the 43 articles described interventions from resource-constrained areas; the majority (35) of the 43 papers and abstracts were from high-income settings. Two articles were from middle-income settings (Argentina and Hong Kong), while six were from resource-constrained settings (Cameroon, Republic of Congo, South Africa, and Thailand). All of the articles were written in English and published in English-language journals with the exception of two, which were written in French and Spanish.

The breakdown by country and paper type (publication versus conference abstract) is given in Table 2. A full list of the papers and abstracts included in the review is available in Annex 2—describing type of intervention, profile of participants, method used for measuring adherence, type of study/method used for measuring impact, pre- and postintervention levels of adherence, country, and results.

Table 2. Papers/Abstracts Included in Literature Review

Country	Publication or Abstract (Number)
Argentina	Abstract (1)
Australia	Publication (1)
Cameroon	Abstract (1)
Congo	Abstract (1)
France	Publication (2)
Hong Kong	Publication (1)
South Africa	Abstract (1)
Spain	Publication (3)
Thailand	Abstract (3)
USA	Publication (17), Abstract (12)

Individuals Targeted by Adherence Interventions

Twenty studies of the interventions to improve adherence to ART captured by the review targeted the general HIV-positive client population (both male and female). In two of these cases, the intervention targeted only women. In all other cases (23), the intervention targeted a specific subgroup of patients, often underserved or marginalized groups.

Examples of client/patient subgroups included—

- Captive population: patients in a prison setting or active/recovering substance use addicts in a treatment facility
- The homeless
- Indigent populations
- Children/adolescents and/or their caregivers
- Populations with a history of poor adherence
- ART-naïve patients or patients who are switching to a new protease inhibitor (PI)

Although interventions targeting providers are not uncommon, at least in developed countries,⁶⁷ none of the literature review papers encountered analyzed the impact of such interventions. However, a few papers did address behavior of caregivers in helping children or adolescents with adherence to ART.

What Methods Are Being Used to Measure Adherence?

A major obstacle encountered in the literature review was that many of the studies aimed at improving adherence acknowledge that no gold standard exists for measuring adherence, although many methods do exist. As a result, most researchers did not present their chosen standard measurement of adherence.

Findings from the literature indicate that many different types or combinations of measures were used in the intervention studies captured. Often, a combination of measures was used and, in a few cases, the method used was not clear (mostly because it was not specified by the author). In the studies reviewed, no method of measuring adherence was linked to achievement of higher rates of adherence or to a particular subgroup of clients on ART (see Annex 2 for a summary of the methods used to measure adherence and the corresponding interventions).

Self-report was the most frequently applied method for measuring adherence, used in 29 of the 43 papers. Sixteen of the studies used HIV RNA viral load counts. Other methods reported included CD4+ counts (8 studies), MEMS caps (5 studies) or other forms of electronic monitoring (2 studies), pill counts (4 studies), and pharmacy refill (1 study).

⁶⁷ Paul Arnow, personal communication, 2004.

How Is “Good Adherence” Defined?

Given that there is presently no agreed-upon “gold standard” or “optimal” adherence level, researchers generally refer to ideal ART adherence as being somewhere in the range of 80 to 100 percent. The evidence from the literature review supports this definition of adherence, with some studies choosing as low as 80 percent^{68,69} as the optimal level, and others as high as 100 percent.⁷⁰

In cases where authors chose to establish a level of adherence to serve as a guide in their research, the authors often added a caveat to their choice of figures. For example, Goujard and colleagues⁷¹ reported a 100 percent adherence level in their study, also pointing out that “it is difficult to measure adherence especially in a randomized study which is intended to improve adherence as measuring adherence itself may be a tool that helps to improve adherence.”

One very interesting and inexplicable finding from the literature review was that most papers did not provide information on either baseline or postintervention levels of adherence. Instead, papers reported only whether adherence had improved or not as a result of the intervention. The amount by which adherence improved was rarely noted. The few cases where the level of improvement was given are listed in Annex 2.

Crucial Issues Considered by Health Care Providers Designing Adherence Interventions

Provider Understanding of Long-Term Adherence

Although none of the papers actually studied the patient-provider relationship as a specific intervention, some researchers⁷² have recommended that establishing a strong and understanding relationship is a crucial factor in understanding or willingness to understand the strains and complications of long-term adherence. Thus, such a relationship is a potential mechanism to assist the patient in attaining higher adherence rates.

In some cases, patient adherence is as confusing for health care providers as it is for patients; consequently, many health care providers are constantly exploring new dimensions to improve a patient’s overall adherence to medications. Providers have even been reported to undergo “mock antiretroviral therapy” to gain perspective.⁷³ It is important to note that providers may not

⁶⁸ S. R. Smith, J. C. Rublein, C. Marcus, et al. A Medication Self-Management Program to Improve Adherence to HIV Therapy Regimens, *Patient Education and Counseling* 50 (2003): 187–99.

⁶⁹ D. L. Jones, M. Ishii, A. LaPerriere, et al. Influencing Medication Adherence among Women with AIDS, *AIDS Care* 15, no. 4 (2003): 463–74.

⁷⁰ C. Goujard, N. Sohler, D. Peyramond, et al. Impact of a Patient Education Program on Adherence to HIV Medication: A Randomized Clinical Trial, *JAIDS* 34, no. 2 (2003): 191–94.

⁷¹ C. Goujard, N. Sohler, D. Peyramond, et al. Impact of a Patient Education Program on Adherence to HIV Medication: A Randomized Clinical Trial, *JAIDS* 34, no. 2 (2003): 193.

⁷² See note 50.

⁷³ M. L. Leider, and G. Kalkut. Understanding Adherence to Medication Adherence, *Annals of Internal Medicine* 132 (2000): 418.

perform any better than patients in adhering to long-term ART.⁷⁴ For example, the reasons cited for provider nonadherence do not differ from those of patients; reasons commonly include inability to follow dietary restrictions, interference of dosing with daily routine, pill burden, and confusion with the exact detail of the regimen.⁷⁵ The literature suggests that providers require more training in adherence counseling; a mock trial such as the one described will arm health care providers with firsthand knowledge of the complications that patients are faced with when aiming to achieve perfect adherence levels.⁷⁶

Personalized Interventions May Be More Effective at Promoting Adherence

Available evidence⁷⁷ points to the fact that in cases where the clients' input was requested to design an intervention, the intervention was very effective in improving adherence. Individualized medication management programs seem to be more effective than generalized programs;⁷⁸ for example, a regimen that is tailored to suit the client's lifestyle and schedule (in terms of dosing times, pill taste and size, and prescription refills) combined with a positive attitude adopted by the patient seems to have a better chance of leading to higher levels of adherence.^{79,80} In addition, evidence⁸¹ supports the argument that a strong support system (familial or peer) is more effective in encouraging adherence than simply providing patients with documentation. Finally, evidence⁸² exists that personalized support interventions increase treatment adherence because poor client-provider communication and less than optimal interaction can lead to a negative client attitude vis-à-vis the provider and, consequently, the treatment. A supportive provider instead may contribute to higher levels of adherence.

Adherence Is a Multifaceted and Complex Issue

Analysis of the factors required to maintain high adherence levels provides evidence that adherence is a multifaceted issue that involves several aspects of the patient's lifestyle choices, which can be further supported or complicated by the physician's approach to counseling and treatment.

⁷⁴ In the study cited, only one of the 35 health care workers who participated in the trial achieved 100 percent adherence (see note 76).

⁷⁵ See note 76.

⁷⁶ C. E. Golin, S. R. Smith, and S. Reif. Adherence Counseling Practices of Generalist and Specialist Physicians Caring for People Living with HIV/AIDS in North Carolina, *Journal of General Internal Medicine* 19, no. 1 (2004): 16–27.

⁷⁷ A. Ammassari, M. P. Trotta, R. Murri, et al. Antinori for the AdICoNA Study Group: Correlates and Predictors of Adherence to Highly Active Antiretroviral Therapy: Overview of Published Literature, *Journal of Acquired Immune Deficiency Syndromes* 31, Suppl. no. 3 (2002): S123–S127.

⁷⁸ A. Molassiotis, V. Lopez-Nahas, W. Y. Chung, et al. A Pilot Study of the Effects of a Behavioral Intervention on Treatment Adherence in HIV-Infected Patients, *AIDS Care* 15, no. 1 (2003): 125–35.

⁷⁹ See note 57.

⁸⁰ See note 68.

⁸¹ See note 39.

⁸² C. Di Iorio, K. Resnicow, M. McDonnell, et al. Using Motivational Interviewing to Promote Adherence to Antiretroviral Medications: A Pilot Study, *Journal of the Association of Nurses in AIDS Care* 14, no. 2 (2003): 52–62.

Interventions that are developed to promote, improve, and enhance adherence should be designed to address the many challenges that patients and providers face in achieving adherence. This involves a great deal of creativity and understanding of the various dimensions that nonadherence could take. Researchers agree that in order to be effective, interventions should be individualized, comprehensive, and repetitive.⁸³ To achieve this aim, most interventions to improve adherence are divided into three main categories: cognitive (designed to teach, clarify, or instruct), behavioral (designed to shape, reinforce, or influence behavior), or affective (designed to optimize social and emotional support).⁸⁴

Evidence of Impact of Different Interventions on Adherence Levels

The next few pages describe the different types of interventions identified and outlined in the papers that were reviewed, and to the extent possible, discusses the evidence supporting their impact on adherence levels.

The following categories of interventions were described in the papers reviewed—

- DOT⁸⁵—also referred to as Directly Administered Antiretroviral Therapy (DAART) or Modified DOT (M-DOT)
- Social support
- Knowledge and counseling
- Financial incentives
- Technological devices
- Multiple combination interventions: includes a combination of the categories described above

Table 3 is a summary of the interventions that are described in the studies.

⁸³ V. E. Stone. Enhancing Adherence to ARVs: Strategies and Regimens, July 25, 2002, <http://www.medscape.com/viewarticle/438193> (accessed Nov. 2004).

⁸⁴ J. M. Simoni, P. Frick, D. Pantalone, et al. Antiretroviral Adherence Interventions: A Review of Current Literature and Ongoing Studies, *Topics in HIV Medicine* 11, no. 6 (2003): 185–98.

⁸⁵ In theory, DOT could be classified as social support; however, given the number of papers and the fact that they tended to target captive populations, the authors chose to keep DOT as a separate category.

Table 3. Summary of Interventions Described in the Studies Researched for the Literature Review⁸⁶

Intervention	Brief Description of Intervention	Number of Studies Using this Method	Success Rate among Studies Using This Method	Outcomes Reported	Comments
DOT	Observation of medication administration by a caregiver or health care worker. Less than 100 percent DOT (observation of all doses) is the chosen method of most DOT studies captured by the review. In these cases of less than 100 percent DOT—M-DOT and Modified-Directly Administered Antiretroviral Therapy (M-DAART)—the presence of another individual is required for some but not all of the doses taken as part of the treatment regimen.	8	7 indicated an improvement in adherence whereas 1 study did not indicate an improvement.	Several of the studies describe DOT among captive populations. One ⁸⁷ recommends DOT as a potentially viable treatment option for recovering substance users who are confined to a treatment facility. In another comparative study, ⁸⁸ patients who underwent DOT were found to have a better virologic response than those who were in the control group. In another study, ⁸⁹ where DOT was not used among a captive population group and an outreach worker was assigned to the patient to observe certain doses, the author reported that even unobserved dosing improved to the point where the patients' baseline HIV RNA levels decreased.	In theory, M-DOT at the health facility level and provided by outreach workers in the community or by family members in the home may be an effective and relatively inexpensive method for improving adherence. ⁹⁰

⁸⁶ Please note that some of the interventions described in this table also include some combination of one or two interventions. A full description of the interventions is available in Annex 2.

⁸⁷ S. Clarke, E. Keenan, M. Ryan, et al. Directly Observed Antiretroviral Therapy for Injection Drug Users with HIV Infection, *AIDS Reader* 12, no. 7 (2002): 305–16.

⁸⁸ M. Fischl, J. Castro, R. Monroig, et al. *Impact of Directly Observed Therapy on Long-Term Outcomes in HIV Clinical Trials*. Abstract 71, 7th Conference on Retroviruses and Opportunistic Infections (January 30–February 2, 2000), San Francisco, CA.

⁸⁹ M. S. Stenzel, M. McKenzie, J. A. Mitty, et al. Enhancing Adherence to HAART: A Pilot Program of Modified DOT, *AIDS Reader* 1, no. 6 (2001): 317–28.

⁹⁰ See Lucas (2001) for further discussion on issues central to DOT/M-DOT for ART.

Intervention	Brief Description of Intervention	Number of Studies Using this Method	Success Rate among Studies Using This Method	Outcomes Reported	Comments
Social support	Interventions where individuals are provided with material support (food, travel support, etc.) or where clinic-based or outreach activities were provided or where some form of community, provider, peer, or familial support was provided.	10	Of the 10 studies that reported using this intervention, 8 reported an increase in adherence and 2 reported no significant improvement in adherence. Importantly 2 of the studies that reported an increase in adherence indicated that the positive outcomes achieved might not be sustainable beyond the period of the intervention.	While one study ⁹¹ states that social support did not considerably improve adherence levels of patients who participated in the intervention, another study, ⁹² which combined counseling with social support provided by the health care provider, observed that the intervention had a significant effect on the viral load of the patient who participated in the intervention.	One can assume that social support specific to the given context might be the most acceptable and desired form of intervention from the patient's perspective. To determine the most appropriate and effective type of social support intervention, patients', caregivers', and community's perspectives must be taken into account.

⁹¹ A. C. Collier, H. Ribaudo, J. Feinberg, et al. *Randomized Study of Telephone Calls to Improve Adherence to ARV Therapy*, Abstract 602, 9th Conference on Retroviruses and Opportunistic Infections (February 24–28, 2002), Seattle, WA.

⁹² L. R. Hirschhorn, L. Ruhlmann, P. B. Lawrence, et al. *Longer Term Impact of a Short Term Adherence Intervention for Highly Active Antiretroviral Therapy (HAART)*, Abstract WePeB5832, XV International AIDS Conference (July 11–16, 2004), Bangkok.

Intervention	Brief Description of Intervention	Number of Studies Using this Method	Success Rate among Studies Using This Method	Outcomes Reported	Comments
Knowledge and counseling	Interventions that seek to improve the knowledge of the participant in the intervention are known as “cognitive” interventions. Several of the “knowledge” interventions encountered fall into this category. Counseling interventions encountered provide some form of education alongside social support.	18	Of the 18 studies that reported using this intervention method, 17 reported that it was successful in improving adherence levels and 1 of the studies reported no success.	One study ⁹³ that provided solely individual counseling reported improving adherence levels among participants. Another study, ⁹⁴ which involved multiple combinations of interventions—including behavior change, patient information, and counseling—was reported not to have had any significant impact on reported adherence levels.	Many studies have shown that providing information is much easier than changing behavior and that knowledge does not necessarily influence action: “Changing people’s behavior generally requires a long-term strategy undertaken after a careful analysis of the situation and identification of priority problems...materials should always be evaluated for their impact not only on knowledge acquired but also on actual behavioral change.” ⁹⁵

⁹³ H. Knobel, J. Alonso, J. L. Casado, et al. Validation of a Simplified Medication Adherence Questionnaire in a Large Cohort of HIV-Infected Patients: The GEEMA Study, *AIDS* 16 (2002): 605–13.

⁹⁴ D. A. Murphy, M. C. Lu, D. Martin, et al. Results of a Pilot Intervention Trial to Improve Antiretroviral Adherence among HIV-Positive Patients, *Journal of the Association of Nurses in AIDS Care* 13, no. 6 (2002): 57–69.

⁹⁵ MSH and WHO. *Managing Drug Supply*, 2nd ed. (West Hartford, CT: Kumarian Press, 1997).

Intervention	Brief Description of Intervention	Number of Studies Using this Method	Success Rate among Studies Using This Method	Outcomes Reported	Comments
Financial incentives	Financial incentives are provided as a reward for either participating in the intervention or achieving positive results during the intervention. In the cases captured by the review, they are usually used in combination with other interventions.	3	All 3 studies that indicated they had used this method of intervention reported success.	During a comparative study ⁹⁶ of three groups of patients, of which one group was given a monetary reward, the authors noted that the group receiving the financial incentive performed better than the other two groups.	While financial incentives may be a strong motivator for behavior change, sustainability concerns are considerable.
Technological devices (reminder devices)	Most studies describing technological devices to enhance adherence classify these devices as reminder devices. Examples include cell phones, pagers, and other portable reminder devices.	9	Of the 9 studies that reported using this method of intervention, 7 indicated that it was successful in improving the adherence outcomes of the patients. Two studies showed that it was not successful.	One comparative study ⁹⁷ reported that two of the technological devices used—cell phones and pagers—have an equally positive effect on improving adherence levels. Another study ⁹⁸ reported an improvement in adherence levels but states that this improvement was not very marked and that more intensive interventions are required in order to improve adherence.	Although these devices were originally assumed not to be not very applicable to resource-constrained settings, the evidence has shown otherwise, at least for some poorer settings, ⁹⁹ and therefore should not automatically be ruled out.

⁹⁶ M. O. Rigsby, M. I. Rosen, J. E. Beauvais, et al. Cue-Dose Training with Monetary Reinforcement: Pilot Study of an Antiretroviral Adherence Intervention, *Journal of General Internal Medicine* 15, no. 12 (2000): 891–3.

⁹⁷ A. Andrade, A. W. Wu, R. L. Skolasky, et al. *Randomized Feasibility Study of a Cell Phone and a Pager as Potential Adherence Enhancing Devices*, Abstract B12064, XV International AIDS Conference (July 11–16, 2004), Bangkok.

⁹⁸ S. A. Safren, E. S. Hendriksen, N. Desousa, et al. Use of an On-Line Pager System to Increase Adherence to Antiretroviral Medications, *AIDS Care* 15, no. 6 2003: 787–93.

⁹⁹ For example, see Megan Lindow, How SMS Could Save Your Life, *Wired News*, November 4, 2004, http://www.wired.com/news/medtech/0,1286,65585,00.html?tw=wn_story_mailer (accessed November 2004). Also see Kaiser Daily HIV/AIDS Report, “Drug Access: *Wired News* Examines How Text Messaging Helping Patients in Developing Countries Manage HIV/AIDS Treatment,” Kaiser Daily Reports, November 8, 2004, http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=26621 (accessed November 2004).

The major limitation of this analysis is that the majority of papers did not specify pre- or postintervention adherence levels: only 4 papers specified baseline adherence levels, while 13 gave postintervention levels. As a result, it was difficult to ascertain which interventions, or combinations thereof, resulted in achieving the best adherence rates. While the analysis is able to address the question of what interventions affect adherence, it does not address the question of what interventions are most successful at improving adherence. Future research is urgently required to address the question of what interventions are most successful, taking into consideration both the type of adherence measurement method used and the intended target adherence level.

Observing and Supervising ART Treatment: Impact of DOT or DAART

Several interventions identified by the literature involved a caregiver or a health care worker who monitors or directly observes most of the patient's doses of ART. This approach, called M-DOT or M-DAART, differs slightly from the DOT approach used for tuberculosis (TB) treatment because not all treatment doses are observed.

While DOT has been a core component of internationally recommended TB control strategy for more than a decade, clear differences exist between treatment of TB and treatment of HIV that need to be taken into consideration in contemplating M-DOT or M-DAART as a potential intervention for improving adherence to HIV treatment. Key differences include the following: TB treatment is for a defined period of time, pill burden is lower, and TB is an airborne disease that allows public health laws to be implemented. Some researchers¹⁰⁰ state that the differences in the treatment options for TB and HIV are a potential threat to the establishment of DOT/DAART for HIV/AIDS treatment programs.

The majority of studies from high-income settings that used M-DOT addressed captive populations and marginalized groups and showed moderate success.^{101,102,103,104} An initial analysis of implementation of DOT in high-income settings led Lucas and colleagues¹⁰⁵ to point out that most of the DOT interventions take advantage of the presence of captive populations who have more frequent contact with health care personnel.

However, not all of the DOT programs in developed countries are implemented using captive populations; in some cases,¹⁰⁶ outreach workers are assigned to patients to observe one daily dose of HIV medication, and other doses are not observed. Depending on the setting, this form of outreach may be more effective than M-DOT in a health facility in developing countries.

¹⁰⁰ G. Lucas, C. W. Flexner, and R. D. Moore. Directly Administered Antiretroviral Therapy in the Treatment of HIV Infection: Benefit or Burden? *AIDS Patient Care and STDs* 16, no. 11 (2002): 527–35.

¹⁰¹ See note 41.

¹⁰² See note 91.

¹⁰³ See note 46.

¹⁰⁴ See note 104.

¹⁰⁵ See note 102.

¹⁰⁶ See note 92.

Findings from the review indicate that experts are divided on the feasibility of DOT as an adherence intervention for resource-constrained settings.^{107,108,109,110} Although little conclusive evidence shows the effectiveness of M-DOT/M-DAART in improving adherence in these settings, evidence indicates that clients are not averse to taking some directly observed doses within either the clinic or the home setting.¹¹¹ There is evidence that, similarly to high-income settings, outreach DOT has been and continues to be used effectively in some resource-constrained settings; for example by the HIV Equity Initiative in Haiti for care of HIV-positive individuals by *accompagnateurs* (or treatment partners).¹¹²

Significantly, DOT for HIV has not been thoroughly tried and tested—to the point where it can be concluded to be a viable intervention—in either high-income or resource-constrained settings. Most of the ideas for implementing DOT in HIV treatment programs come from experiences with TB treatment programs. Analyzing the differences between implementation of DOT for TB treatment in high-income settings and resource-constrained settings, Stevens and colleagues¹¹³ point out that DOT for TB treatment had mixed results in resource-constrained settings in sub-Saharan Africa. Citing examples of low treatment completion rates of 37 percent to 78 percent¹¹⁴ and problems associated with implementing DOT programs in resource-constrained settings reported in studies,¹¹⁵ such as lack of sufficient funds for travel to and from treatment centers, poor medicine supply, and lack of resources to supervise treatment, the authors recommend that the model of DOT used in developed countries (which have achieved moderate success) should not be a yardstick to measure the potential treatment outcome of using DOT in resource-constrained settings. They recommend that thorough modifications need to be made to DOT for HIV treatment before it is avidly advocated in resource-constrained settings.

Impact of Social Support Interventions

Social support can take many forms. For the purposes of this review it is defined to include material things (such as food and travel support); clinic-based or outreach activities (such as home visits or regular telephone check-ins); and the less tangible form of community, provider, or family warmth and support. Social support is a key factor in management of other chronic diseases; for example, it has played a key role in TB-DOTS programs in some Russian oblasts in

¹⁰⁷ W. Woodward. Should Directly Observed Therapy Be Considered for Treatment of HIV? *Journal of the American Medical Association* 276, no. 24 (1996): 1956.

¹⁰⁸ See note 22.

¹⁰⁹ C. A. Liechty, and D. R. Bangsberg. Doubts about DOT: Antiretroviral Therapy for Resource-Poor Countries, *AIDS* 17, no. 9 (2003): 1383–87.

¹¹⁰ See note 22.

¹¹¹ E. A. Talbot, S. Halabi, R. Manchanda, et al. Knowledge, Attitudes and Beliefs about Directly-Administered Antiretroviral Therapy among Tuberculosis Patients, Botswana, *International Journal on STDs & AIDS* 15, no. 4 (2002): 282–83.

¹¹² P. Farmer, F. Leandre, J. Mukherjee, et al. Community-Based Treatment of Advanced HIV Disease: Introducing DOT-HAART, *Bulletin of WHO* 79, no. 12 (2001): 1145–51.

¹¹³ See note 22.

¹¹⁴ M. Zwarenstein, J. H. Schoeman, C. Vundule, et al. Randomized Controlled Trial of Self-supervised and Directly Observed Treatment of Tuberculosis, *The Lancet* 352 (1998): 1340–1343.

¹¹⁵ S. J. O’Boyle, J. J. Power, M. Y. Ibrahim, et al. Factors Affecting Patient Compliance with Anti-Tuberculosis Chemotherapy Using Directly Observed Treatment, Short-Course Strategy (DOTS), *The International Journal of Tuberculosis and Lung Disease* 6, no. 4 (2002): 307–12.

recent years¹¹⁶ and has contributed to higher adherence rates among adolescents with diabetes.¹¹⁷ In a recent review, one author finds that “patients with supportive friends and families tend to adhere to HAART [highly active antiretroviral therapy] better than those without these supports.”¹¹⁸ Social support has also been shown to be effective in HIV-positive populations considered to have more difficulty adhering to long-term treatment, such as highly infected drug users.¹¹⁹

Several studies encountered in the literature review emphasize the importance of the presence of another individual, either a fellow person living with HIV/AIDS¹²⁰ or a peer or family member.¹²¹ The presence of another individual who encourages and monitors the patient’s medication-taking can have a positive influence on adherence and can be a key component of social support. Reports from the Haiti Equity HIV Project,¹²² managed by the nongovernmental organization Partners in Health, indicate that the role of the *accompagnateurs* makes a significant difference in the patient’s ability to adhere to medication and, consequently, on treatment outcomes. *Accompagnateurs* not only encourage medication-taking, but also assist in other household chores and family duties that the patient might be too ill to carry out.

Social support provided by peers whom the patient can relate to, who have had similar experiences, and who are faced with similar challenges can help a patient improve adherence.¹²³ One study found that “the most enduring and successful behavioral interventions are those that affect group norms and members’ willingness to enforce them because they take advantage of a powerful force—peer pressure.”¹²⁴ Organized peer-group interventions should therefore be considered as a potential adherence improvement option.

The development of a social support network has the potential to reduce feelings of isolation among patients who may have difficulty adhering properly to medication. One such example is described in a study¹²⁵ of the development of a theater workshop in Harlem, New York, that entailed the hands-on involvement of PLWHA. The workshop was part of an adherence support program already in progress, aimed at getting patients to associate with each other and identifying common experiences and barriers to adherence. The forum enabled patients to share

¹¹⁶ See summaries on the Russian oblasts of Ivanovo, Orel, and Novgorod on www.msh.org/rpmpplus/tb (click on “Incentives and Enablers” and then click on “Search I&E by region and country” located in the “Highlights” box).

¹¹⁷ R. Shillitoe, and M. Christie. Psychological Approaches to the Management of Chronic Illness: The Example of Diabetes Mellitus, in *Current Developments in Health Psychology*, ed. P. Bennett, J. Weinman, and P. Spurgeon (London: Harwood Academic, 1990).

¹¹⁸ See note 37.

¹¹⁹ See note 41.

¹²⁰ S. Kongsawat, J. Pinpetech, S. Reungde, et al. *People Living with HIV/AIDS: A Living Tool for Adherence*, Abstract MoOrD1025, XV International AIDS Conference (July 11–16, 2004), Bangkok.

¹²¹ M. E. Lyon, C. Trexler, C. Akpan-Townsend, et al. A Family Group Approach to Increasing Adherence to Therapy in HIV-Infected Youths: Results of a Pilot Project, *AIDS Patient Care and STDs* 17, no. 6 (2003): 299–308.

¹²² See note 9.

¹²³ See note 41.

¹²⁴ See note 41.

¹²⁵ A. Hofmann, K. Vanderpuye, H. Williams, et al. *Participatory Theatre as a Novel Approach for Addressing Barriers to Antiretroviral Adherence in Harlem, NY*, Abstract MoPeF3963, XIV International AIDS Conference (July 7–12, 2002), Barcelona.

their experiences and develop a support network that would be useful, especially for those who had no other form of social support in terms of family and friends.

Another example of how patients consider the role of social support as an important aspect in the adherence process is that of the *kōkua* (primary caregivers) within the Hawaiian community.¹²⁶ In one study, patients acknowledged the importance of the presence of the *kōkua*, with one patient emphasizing that the *kōkua* ensured that medication was taken and meals were eaten. Although the report does not indicate that an improvement in adherence levels occurred, patient testimony indicates the importance of the presence of another individual in the process as a positive element that may facilitate adherence.

Role of Education, Information, and Counseling Interventions

Increasing client, and sometimes caregiver and/or provider, knowledge is one underlying component of many interventions to improve ART adherence encountered in the literature. Cognitive interventions, for example, seek to improve the knowledge of a participant in the intervention. This factor is particularly important in HIV treatment where a clear comprehension of the various forms infection can take, as well as the role of treatment in maintaining a good quality of healthy well-being, may be key aspects of continuing treatment. Indeed, some experts have argued that “understanding the relationship between adherence and viral load and between viral load and disease progression is integral to adherence behaviors.”¹²⁷ While “knowledge” does not necessarily translate into “belief,” it is one step toward achieving this goal.

Detailed knowledge of how ART works may not be necessary to promote adherence; instead, in some communities, the belief that ART may prolong life and postpone death may be sufficient to promote high adherence. Initial evidence¹²⁸ from developed countries supports this notion: adherence has been found to be greater among those who believe ART is effective.

Knowledge of and belief in ART may be promoted through educational interventions, which can take the form of individualized or group sessions; which may involve only patients; or which may include caregivers, providers, community members, or some combination thereof. They can be “uni-directional” (with the “teacher” providing the information to the “students”) or involve a more participatory approach. The literature highlights the importance of using tools and techniques that the patient can relate to and will not perceive as unfamiliar.¹²⁹ Educational interventions can take place prior to ART initiation¹³⁰ (offering an opportunity to provide information about side effects and guidance for treatment), at the beginning of therapy, or at later intervals, or the educational interventions can be ongoing. In some cases evidence indicates ongoing educational interventions may have the highest long-term impact.¹³¹

¹²⁶ L. Ka’Opua and C. W. Mueller. Treatment Adherence among Native Hawaiians Living with HIV, *Social Work* 49, no. 1 (2004): 55–63.

¹²⁷ See note 37.

¹²⁸ See note 57.

¹²⁹ A. M. Fourny, and M. L. Williams. Formative Evaluation of an Intervention to Increase Compliance to HIV Therapies: The ALP Project, *Health Promotion Practice* 4, no. 2 (2003): 165–70.

¹³⁰ See note 113.

¹³¹ See note 73.

Most of the studies identified through the literature review that describe interventions to improve knowledge are usually combined with other behavioral and support interventions. Counseling, a form of educational and social support, is promoted in the literature as a potential mechanism for improving adherence¹³² and, when combined with education, is the underpinning strategy of a number of interventions. Counseling and education are often delivered in combination by a health professional and an HIV-positive peer.¹³³

Some ART adherence educational/counseling interventions are based on already existing theories. One example is an intervention that uses the “self-efficacy theory,” a theory built on the belief that a person is capable of organizing and executing a course of action required to perform a particular activity.¹³⁴ Studies^{135,136} have shown that this individualized personalized approach, which strives to boost client morale, skill development, and self-sufficiency, can have a significant short-term effect on adherence to treatment.

Several of the interventions that involve an educational/counseling strategy also use a technique called “motivational interviewing” (MI), which may be very effective in promoting adherence to ART. Motivational interviewing is defined as “a client-centered, goal-directed counseling style”¹³⁷ and was originally developed to treat substance abuse and later adapted to a wide spectrum of health behavior change interventions. It has shown success in various types of behavior modification programs¹³⁸ and serves to promote patients’ enthusiasm and self-assurance. Because the technique is “client-centered,” it provides a forum for patients to participate actively and identify underlying problems and barriers to treatment adherence. MI is used by a number of studies^{139,140,141} in the papers reviewed as part of a counseling strategy.

Impact of Financial Incentives

When providing financial incentives to patients in exchange for taking medications, ethical concerns come into play; will the patients be taking the medications because of the perceived potential reward or because they believe that they have a chance to improve their health?

¹³² See, for example, C. Pradier, L. Bentz, B. Spire, et al. Efficacy of an Educational and Counseling Intervention on Adherence to Highly Active Antiretroviral Therapy: French Prospective Controlled Study, *HIV Clinical Trials* 4 (2003): 121–31.

¹³³ Ibid.

¹³⁴ A. Bandura, *Self-Efficacy: The Exercise of Control* (New York: Freeman, 1997), 79–115.

¹³⁵ See note 71.

¹³⁶ See note 39.

¹³⁷ M. S. Adamian, C. E. Golin, L. A. Shain, et al. Brief Motivational Interviewing to Improve Adherence to ART: Development and Qualitative Pilot Assessment of an Intervention, *AIDS Patient Care and STDs* 18, no. 4 (2004): 229–38.

¹³⁸ W. Miller and S. Rollnick, *Motivational Interviewing: Preparing People to Change Addictive Behavior* (New York, NY: The Guildford Press, 1991).

¹³⁹ S. A. Safren, M. W. Otto, J. L. Worth, et al. Two Strategies to Increase Adherence to HIV Antiretroviral Medication: Life-Steps and Medication Monitoring, *Behaviour Research and Therapy* 39 (2001): 1151–62.

¹⁴⁰ See note 139.

¹⁴¹ See note 85.

Although provision of financial incentives has been reported in the literature as a strategy to enroll and maintain patients in (primarily preventive) HIV/AIDS services,^{142,143,144} little evidence was found of financial incentives being used as a mechanism to improve adherence to ART. The two examples in the studies were in high-income settings and provided evidence that financial incentives may have the potential to improve adherence to treatment. Yet, given that one study¹⁴⁵ was an uncontrolled pilot and the other¹⁴⁶ revealed that adherence levels were not maintained following the intervention period, more research on the long-term effectiveness of financial incentives is required. In one of the studies, the authors point out that, among the group of patients receiving the intervention in addition to a financial reward, “the rapid improvement suggests that the motivating effect of the reinforcement rather than new skill acquisition.”¹⁴⁷

Impact of Technology Interventions

In several of the high-income setting studies identified by the literature review, study participants’ were given devices or instruments that served as reminders to trigger the patient to take the required dose of the medication at a certain time. Often these devices—which involve minimal health care staff time—played an integral role in improving adherence.¹⁴⁸ Some authors¹⁴⁹ even argue that using communication devices—pagers, alarms, and telephones—can have more impact on improving adherence than interventions using education, counseling, or additional supervision strategies. Others,¹⁵⁰ however, have found that use of telephone calls as a reminder mechanism and as social support is not an effective strategy for promoting adherence—in that case, however, the fact that a “standardized script” was followed may have rendered the intervention less personalized and less effective.¹⁵¹

While many of the communications devices identified had a positive impact on client adherence levels, the feasibility of these interventions in resource-constrained settings is unclear. Given that these communications devices often depend on a level of technology and infrastructure that is common in high-income settings, yet often unavailable in resource-constrained settings, one might think that their widespread introduction may not be a feasible option in the latter. Nevertheless, a few local initiatives using technological interventions to improve adherence to ART were identified in resource-constrained settings by the literature review. The most notable

¹⁴² S. Deren, R. Stephens, W. R. Davis, et al. The Impact of Providing Incentives for Attendance at AIDS Prevention Sessions, *Public Health Reports* 109 (1994): 548.

¹⁴³ M. Kamb, L. MacGowan, F. Rhodes, et al. *Developing an HIV Prevention Intervention for a Randomized Trial*, Abstract WCS21-1, V International Conference on AIDS (June, 1993), Berlin, Germany.

¹⁴⁴ J. Greenberg, J. Lifshay, N. van Devanter, et al. Preventing HIV Infection: The Effects of Community Linkages, Time and Money on Recruiting and Retaining Women in Intervention Groups, *Journal of Women's Health* 7 (1998): 587–96.

¹⁴⁵ J. D. Bamberger, J. Unich, P. Klein, et al. Helping the Urban Poor Stay with Antiretroviral HIV Drug Therapy, *American Journal of Public Health* 90 (2000): 5.

¹⁴⁶ See note 98.

¹⁴⁷ Ibid.

¹⁴⁸ See note 45.

¹⁴⁹ P. J. Dunbar, D. Madigan, L. A. Grohskopf, et al. A Two-Way Messaging System to Enhance Antiretroviral Adherence, *Journal of American Medical Association* 10 (2003): 11–15.

¹⁵⁰ See note 93.

¹⁵¹ Unfortunately, the effect of the “script” was impossible to ascertain from the abstract in question.

example is in South Africa where the “On-Cue” initiative¹⁵² is using “smart pill boxes” to monitor adherence through a central server. The process also involves sending text messages to targeted patient as reminders, or using the mobile phone network and text messaging, to improve reporting and case management (including adherence) during HIV-positive patient outreach through the Sizophila project in Cape Town.¹⁵³ Although the technological intervention proved effective, other unforeseen problems arose: health care workers involved in the adherence program were victims of cell phone robberies, and the program had to be modified accordingly—health care workers now leave their cell phones at home while making their routine visits.

Impact of Multiple Interventions

Findings from the literature review substantiate the fact that programs are choosing multifaceted interventions in order to improve adherence. In many cases reviewed, the intervention is in fact a combination of interventions, combining elements from one or more of the interventions previously mentioned. This strategy is recommended by several authors,¹⁵⁴ who point out that interventions that involve a combination of these categories produce better adherence results than an intervention that only includes one category. In some settings, a higher number of adherence aids may possibly result in higher levels of adherence.¹⁵⁵

The literature review shows that little evidence exists regarding the effectiveness of specific intervention combinations. However, one author¹⁵⁶ hypothesizes that reminder devices may function more effectively if supplemented with training and strengthened case management. Another author¹⁵⁷ argues that a multifaceted approach comprising a number of social support interventions may be the most effective approach. A third¹⁵⁸ highlights the fact that “emerging evidence suggests adherence interventions should employ a multidisciplinary effort involving health care providers, social support networks, family and friends.” Combinations of interventions that complement each other to improve adherence should therefore be considered, while striving to capture not only the effectiveness of the combined multi-intervention but also the particular effectiveness of the different components of the multiple adherence interventions.

What Will Work in Resource-Constrained Settings?

The majority of studies analyzed as part of the literature review are based in high-income settings where health care providers have access to advanced technological devices (electronic reminders, pagers, etc.) and sophisticated tools to measure adherence (MEMS caps for example).

¹⁵² Response from private association, “on-cue,” from South Africa. See SIMpill homepage, <http://www.on-cue.co.za/> (accessed Apr. 2004).

¹⁵³ See note 101.

¹⁵⁴ D. L. Roter, J. A. Hall, R. Merisca, et al. Effectiveness of Interventions to Improve Patient Adherence: A Meta-Analysis, *Med Care* 36 (1998): 1138–61.

¹⁵⁵ C. E. Golin, H. Liu, R. D. Hays, et al. A Prospective Study of Predictors of Adherence to Combination Antiretroviral Medication, *Journal of General Internal Medicine* 17, no. 10 (2002): 756–65.

¹⁵⁶ See note 44 and note 141.

¹⁵⁷ See note 123.

¹⁵⁸ B. J. Turner. Adherence to Antiretroviral Therapy by Human Immunodeficiency Virus-Infected Patients, *Journal of Infectious Diseases* 15, no. 185, Suppl. no. 2 (2002): S143–51.

However, in many resource-constrained countries literacy levels may be low and replacement parts for technological devices may not be readily available; yet some examples cited previously have shown that similar interventions can, under certain circumstances, be successfully implemented in resource-constrained settings.

The human and infrastructure constraints differentiating resource-constrained settings from high-income settings need to be taken into consideration when developing adherence interventions. For example, in the case of interventions that require the establishment of a support network (familial or otherwise), poverty levels in some settings may mean that hospitality has been stretched thin and the fact that a friend or family member falls ill with a debilitating disease does not mean that people will automatically come to his or her assistance. This factor is especially true in cases where even the smallest member of a family has to contribute to the overall family income: there might not be time or people to spare to supervise and monitor correct medication adherence. In some settings, health care workers may be too overwhelmed with patients' needs to spare additional time to implement interventions that require additional effort. In addition, health care workers may not have the time to spare for additional training required for the implementation of certain interventions.

This is not to say that interventions described in the literature review that have been successfully implemented in high-income settings will not work in resource-constrained settings. Implementation of similar measures will simply require additional commitment and effort to understand the local and individual circumstances in order to ensure that the desired results—optimum levels of adherence, reduction in viral load, and improved health outcomes—are achieved.

Constraints

As mentioned previously, 21 of the 43 intervention studies identified were not published papers but abstracts, usually of ongoing work. The information those documents provided was therefore limited, especially with regard to methodology and findings. Although questions existed about whether to include a particular paper or abstract that might not have as rigorous a methodology as preferred or where the degree of rigor was unclear, the authors decided to include them because of the paucity of literature on interventions to improve adherence to ART in general, especially with regard to studies from resource-constrained settings.

Some of the more specific concerns are as follows—

- Lack of a rigorous methodology: Several of the papers were not randomized controlled trials (RCTs).
- Small sample size: For those studies that followed a rigorous methodology, sample sizes were rather small. The sample size of two studies was unclear. In summary, the sample size of the 41 papers follows—

Number of papers	Sample size
20	<50
28	<100
32	<150
37	<200
4	244, 282, 326, and 928

DISCUSSION

The following section highlights and analyzes key findings from the literature review, extrapolating issues relevant to HIV/AIDS treatment programs in developing countries. To the extent possible, it also attempts to identify lessons from experience in high-income settings that might be taken into consideration to guide development of appropriate and effective interventions in resource-constrained settings. Finally, it aims to set out a research agenda, identifying urgent areas in need of more evidence.

Implementation of Multifaceted Interventions to Improve ART Adherence

The literature review provides evidence that interventions presently being planned or used to improve adherence primarily target the patient, while a few target providers, caregivers, or other family members. Examples of such interventions include food and/or travel support, adherence aids, HIV/AIDS case management, telephone calls, monetary incentives, outreach visits, M-DOT, or organized education sessions.

Other innovative approaches exist and should be considered within each given local context: one example already referred to is the use of participatory theater to increase adherence and enhance social support.¹⁵⁹ In some places in the United States, ART provision and promotion of adherence have become a “lucrative business”: incentives such as cell phones, free fax machines, and pagers are provided to clients who choose to purchase their medications from a given pharmacy.¹⁶⁰

Findings from the literature review substantiate the multifaceted nature of optimal interventions: in most cases the intervention is in fact a combination of interventions. The survey findings, while not showing intervention impact, indicate that programs have, for the most part, selected multifaceted approaches to address the issue of ART treatment adherence.

Impact of Individual Adherence Interventions and Combinations

Unfortunately, little can be concluded about the individual or cumulative effect of different interventions to improve adherence. Few literature review papers were scientifically rigorous enough to permit solid conclusions to be drawn. From the literature review, one can conclude that a number of interventions seem to affect adherence, but because pre- and postintervention adherence levels were rarely provided, statements cannot be made about one intervention resulting in a higher impact than another, even within a given population. Frequently a combination of interventions was used, making it difficult to determine the individual impact of a given intervention. In addition, adherence measures often differ, or a combination is used, further complicating standardization.

¹⁵⁹ See note 127.

¹⁶⁰ http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=23276 (accessed April 2004).

Nonetheless, the literature review identified several interventions—ranging from social support to DOT and educational interventions to technological or financial interventions—that seem to have a positive impact on adherence, and implementing and evaluating these interventions is the first step toward achieving improved adherence.

Positive Impact of Improved Organization of Services

One U.S.-based study¹⁶¹ found that when adherence services are offered at sites that provide usual HIV medical care (such as hospitals and community-based clinics) higher levels of adherence are reported among clients on ART. The authors attribute this perceived positive result to the assumption that more frequent communication occurs between adherence staff and the client's medical provider than in settings where services are not located at the same site, and that this, in turn, results in closer patient monitoring and higher ART adherence levels.

Ongoing Interventions May Prove More Effective

While most studies captured by the literature review were short-term interventions, many of which showed a positive impact on levels of ART adherence, in some cases^{162,163} the impact of the intervention wore off over time. Some¹⁶⁴ suggest that peaks and valleys exist in adherence and, therefore, interventions may be more effective if sustained over time. More research needs to take place to determine what factors motivate and demotivate patients over time and what period of frequency is most effective for a given intervention and given population. Possibly the most-effective interventions are those that are ongoing—further research is urgently needed concerning this area.

Interventions Must Be Context-Specific and Culturally Appropriate

In many cases, cultural factors may contribute to poor adherence. Several authors^{165,166,167} stress the importance of developing culturally relevant and appropriate interventions to promote

¹⁶¹ L. Weiss, M. Waters, J. Netherland, et al. *The Role of Social Support in Adherence Services: The Client's Perspective*, Abstract WePeB5836, XV International AIDS Conference (July 11–16, 2004), Bangkok.

¹⁶² See note 53.

¹⁶³ T. Wall, J. L. Sorensen, S. L. Batki, et al. Adherence to Zidovudine (AZT) among HIV-Infected Methadone Patients: A Pilot Study of Supervised Therapy and Dispensing Compared to Usual Care, *Drug and Alcohol Dependence* 37 (1995): 261–69.

¹⁶⁴ See note 45.

¹⁶⁵ See, for example:

- J. E. Kemppainen, R. E. Levine, M. Mistal, et al. HAART Adherence in Culturally Diverse Patients with HIV/AIDS: A Study of Male Patients from a Veteran's Administration Hospital in Northern California. *AIDS Patient Care and STDs* 15, no. 3 (2001).
- L. Ka'Opua. Treatment Adherence to an Antiretroviral Regime: The Lived Experience of Native Hawaiians and Kōkua, *Pacific Health Dialogue* 8, no. 2 (2001): 290–98.
- L. Ka'Opua and C. W. Mueller. Treatment Adherence among Native Hawaiians Living with HIV, *Social Work* 49, no. 1 (2004): 55–63.

adherence. Qualitative studies such as focus groups and interviews with patients can help program managers determine what patients consider key barriers to adherence and assist in identifying locally appropriate interventions that patients feel will assist with maintaining high levels of ART adherence.

The client's individual circumstances need to be carefully taken into consideration, along with the context and culture. How can one convince a woman in a developing-country setting to adhere to preventive therapy for her soon-to-be-born child under circumstances where she has no guarantee of treatment for herself? An understanding of the context and the culture in question is crucial.

How to Reward Good Adherence?

One idea for rewarding good adherence is to allow those who have shown good adherence to come less frequently for DOT, for education sessions, or for collection of the next set of pills. For example, a client who has been coming on a daily basis, except for weekends, who shows excellent adherence, could be rewarded by having to attend the clinic to pick up his or her medications three times a week and then twice a week and, ultimately, once a week. Such a process transfers the decision-making power and management of the adherence process from the provider to the client and serves as a mechanism to motivate the client toward higher or perfect levels of adherence. For this strategy to work, a strong measure for accurately assessing adherence is essential.

Critical Need for Evaluation of Impact of Interventions to Promote Adherence to ART

Only one paper¹⁶⁶ captured by the literature review addressed the issue of cost-effectiveness, finding that “in patients with lower baseline levels of adherence or advanced disease, even very expensive, moderately-effective adherence interventions are likely to confer cost-effectiveness benefits that compare favorably with other interventions.” It is remarkable that so little information is available on the cost-effectiveness of interventions to improve adherence to ART, given that ART adherence, at least in developed countries, has been a challenge for many years. As mentioned previously, however, only in recent years has the literature become richer with respect to interventions to improve adherence to ART. An urgent need exists to analyze and compare the cost-effectiveness of those interventions that have been shown to be effective. This step is critical for informing the planning and decision-making process of program managers and policy makers in both developed and developing countries.

¹⁶⁶ J. Martin, G. M. Sabugal, R. Rubio, et al. Outcomes of a Health Education Intervention in a Sample of Patients Infected by HIV, Most of Them Injection Drug Users: Possibilities and Limitations, *AIDS Care* 13, no. 4 (2001): 467–73.

¹⁶⁷ K. M. Melbourne. The Impact of Religion on Adherence with Antiretrovirals, *Journal of the Association of Nurses in AIDS Care* 10, no. 3 (1999): 99–100.

¹⁶⁸ S. J. Goldie, A. D. Paltiel, M. C. Weinstein, et al. Projecting the Cost-Effectiveness of Adherence Interventions in Persons with Human Immunodeficiency Virus Infection, *American Journal of Medicine* 115 (2003): 632–41.

Future Adherence Research: Critical Areas

Findings from the literature review and survey point to a number of urgent research questions around the issue of ART adherence, which include—

- To what extent is adherence really a problem in developing countries? To what extent might it become a problem as ART becomes more widely available and accessible?
- What are ideal adherence rates in developing countries? Should programs be aiming for 100 percent adherence?
- What are the most feasible and cost-effective methods to measure and monitor adherence in resource-constrained settings?
- Of the interventions that seem to improve adherence, which have a higher impact? What adherence rates do they manage to achieve? Which are most cost-effective in each given setting? How might they best be adapted to suit particular circumstances?

CONCLUSION

This paper is a first attempt to understand and catalogue interventions being used to improve long-term adherence to ART.

ART availability and cost are the most immediate and most prohibitive barriers to HIV/AIDS services and treatment, directly inhibiting client access to and continuation of therapy. The extent to which ART adherence is or will become a problem in settings where it is not yet readily available is unclear because adherence data from developing countries is inadequate to draw concrete conclusions. Nevertheless, one can hypothesize that, under most circumstances, interventions should be considered from the outset to assist clients with ART adherence because of the high potential for challenges to long-term adherence and the individual, social, and public health consequences of poor adherence.

As ART becomes more widely available, this paper calls on those considering design and implementation of interventions to encourage higher levels of testing and uptake of preventive therapy and to improve long-term adherence to ART to take the following steps—

- Document those experiences
- Rigorously evaluate the experiences
- Disseminate their findings widely

Only on the basis of such evidence can those responsible for making and implementing policy determine which interventions are most effective and most cost-effective and under what circumstances they should be used. The result will be more people managing their lives successfully while living with HIV/AIDS.

ANNEX 1. TERMS FOR LITERATURE SEARCH

Literature Review Articles

Behavior and Behavior Mechanisms (MeSH) AND ART	=	5898
Behavior and Behavior Mechanisms (MeSH) AND ARV	=	35
Behavior and Behavior Mechanisms (MeSH) AND antiretroviral therapy	=	1343
Behavior and Behavior Mechanisms (MeSH) AND Antiretroviral therapy, highly active (MeSH)	=	620
Behavior and Behavior Mechanisms (MeSH) AND antiretroviral agents (MeSH)	=	1485
Health behavior (MeSH) AND ART	=	140
Health behavior (MeSH) AND antiretroviral therapy	=	782
Health behavior (MeSH) AND Antiretroviral therapy, highly active (MeSH)	=	398
Health behavior (MeSH) AND antiretroviral agents (MeSH)	=	866
Patient acceptance of health care (MeSH) AND ART	=	250
Patient acceptance of health care (MeSH) AND ARV	=	18
Patient acceptance of health care (MeSH) AND antiretroviral therapy	=	843
Patient acceptance of health care (MeSH) AND Antiretroviral therapy, highly active (MeSH)	=	418
Patient acceptance of health care (MeSH) AND antiretroviral agents (MeSH)	=	917

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- The MESH term “Behavior and Behavior Mechanisms” includes “Health Behavior,” “Treatment Refusal,” and the following—
 - Patient noncompliance
 - Patient refusal of treatment
 - Patient non-adherence
 - Patient non-compliance
 - XV International Conference on HIV/AIDS 2004 Abstracts
 The search was conducted on the International AIDS Society website <http://www.iasociety.org/ejias/search.asp?search=adherence&searchtype=6&image1.x=51&image1.y=4> using the search term “adherence,” which produced 170 articles. The authors chose the relevant articles that addressed interventions to improve adherence to HIV treatment, reducing the number of articles to 17.

ANNEX 2. ARTICLES REVIEWED

	Publication Details/ Country	Type of Intervention	Profile of Participants	Method Used for Measuring Adherence	Type of Study/Method for Measuring Impact	Pre- and Postintervention Levels of Adherence	Results
1	<p>Andrade, A., et al. <i>Intervention Trial Using a Novel Electronic Device in HAART Indicators: Impact of Cognitive Dysfunction</i></p> <p>8th Conference on Retroviruses and Opportunistic Infections, 2002, Chicago, IL [Abstract 602]</p> <p>USA</p>	A portable reminder device that also records dosing times (called DMAS)	HIV-positive individuals (N = 35)	MEMS caps and DMAS	RCT	Postintervention adherence level: ≥95% for DMAS users with cognitive impairment	Improvement in adherence among intervention group members.
2	<p>Andrade, A., et al. <i>Randomized Feasibility Study of a Cell Phone and a Pager as Potential Adherence Enhancing Devices</i></p> <p>XV International AIDS Conference, 2004, Bangkok [Abstract B12064]</p> <p>USA</p>	Reminder device using cell phones vs. pagers	HIV-positive individuals on HAART (N = 20)	Self-report	Randomized study	Not stated	Results suggest that both reminder device interventions may positively affect adherence. Neither intervention was considered more effective than the other.

	Publication Details/ Country	Type of Intervention	Profile of Participants	Method Used for Measuring Adherence	Type of Study/Method for Measuring Impact	Pre- and Postintervention Levels of Adherence	Results
3	Ballive-Cassaux, M., et al. <i>Adherence: Therapeutic Group Interventions with Discordant Couples</i> XV International AIDS Conference, 2004, Bangkok [Abstract WePeB5841] Argentina	Psychosocial intervention working with each partner of a discordant couple	Discordant couples (N = 12 couples)	Self-report, CD4+ and HIV RNA levels	Pre-post study	Not stated	Communication among discordant couples may be a key element in adherence.
4	Bamberger, J. D., et al. Helping the Urban Poor Stay with Antiretroviral Drug Therapy <i>American Journal of Public Health</i> , 2000, 90:5 USA	Financial incentives: weekly USD 10 and reminder device (pager)	HIV-positive individuals who are marginalized: homeless	Unclear (self-report?)	Uncontrolled pilot study	Not stated	64% of patients had HIV RNA levels less than 500 after 2 months.

	Publication Details/ Country	Type of Intervention	Profile of Participants	Method Used for Measuring Adherence	Type of Study/Method for Measuring Impact	Pre- and Postintervention Levels of Adherence	Results
5	<p>Blasco, P. <i>Improving Adherence to ART in Children in Resource-Limited Settings</i></p> <p>International Conference on Improving the Use of Medicines (ICIUM), 2004, Chiang Mai, Thailand [Abstract HI001]</p> <p>Thailand</p>	Social support (home visits: prior to ART initiation, when regimen is changed, and hotline support); education sessions	Children and their parents or caregivers (N = 77 children)	Self-report	Unclear	Adherence levels at the end of 3 months of intervention as reported by caregivers: >95% (N = 66); at the end of 12 months: >95% (N = 47)	Regular assessment of adherence, especially at the beginning of the treatment...allows the prompt identification and planned intervention for nonadherent children on ART.
6	<p>Broadhead, R., et al. Increasing Drug Users' Adherence to HIV Treatment: Results of a Peer-Driven Intervention Feasibility Study</p> <p><i>Social Science Medicine</i>, 2002, 55(2):235–46</p> <p>USA</p>	Social (peer) support and counseling for which “secondary incentives” (nominal monetary rewards) were received for positive outcomes (appointments kept, prescriptions picked up on time, etc.)	HIV-positive active drug users (N = 14)	Pill counts	Uncontrolled pilot study	Overall postintervention score: 90%	Mean adherence was 90% at 9 weeks.

	Publication Details/ Country	Type of Intervention	Profile of Participants	Method Used for Measuring Adherence	Type of Study/Method for Measuring Impact	Pre- and Postintervention Levels of Adherence	Results
7	Caprio, M., et al. <i>Closely Supervised Intervention Pilot Program to Improve Adherence among Urban Indigent Women</i> XIV International AIDS Conference, 2002, Barcelona [Abstract WePeB5857] USA	MI, counseling, education, reminder devices, and home visits	Urban indigent woman (N = 39)	Self-report, pharmacy refills, clinic visits, and lab data to assess viral load	Comparison group	Baseline adherence levels (preintervention): 67% among ART- experienced patients; 90–92% at the end of week 4 of intervention; 98– 100% among ART- naïve patients at the end of week 8	An intensive adherence coordination team intervention resulted in successful short-term virologic response in hard-to-reach patients.
8	Clarke, S., et al. Directly Observed Antiretroviral Therapy for Injection Drug Users with HIV Infection <i>The AIDS Reader</i> , 2002, 12(7):305–16 USA	DOT	Recovering substance abusers (captive population) (N = 39, 24 men and 15 women)	CD4+ cell counts and HIV RNA levels	Prospective observation study	Not stated	DOT should be considered a potential option for providing HAART to IDUs, particularly when used in conjunction with methadone maintenance therapy.

	Publication Details/ Country	Type of Intervention	Profile of Participants	Method Used for Measuring Adherence	Type of Study/Method for Measuring Impact	Pre- and Postintervention Levels of Adherence	Results
9	Collier, A. C., et al. <i>Randomized Study of Telephone Calls to Improve Adherence to ARV Therapy</i> 9th Conference on Retroviruses and Opportunistic Infections, 2002, Seattle, WA [Abstract 602] USA	Social support (increased telephone contact with patients)	282 HIV- positive individuals (N = 282, 80% male)	Self-report and HIV RNA levels	Randomized substudy of a large multicenter comparative ART trial	Not stated	Enhanced telephone contact did not enhance levels of reported adherence or improve virologic outcomes.
10	Di Iorio, C., et al. Using Motivational Interviewing to Promote Adherence to Antiretroviral Medications: A Pilot Study <i>Journal of the Association of Nurses in AIDS Care</i> , 2003, 14(2): 52–62 USA	Nursing intervention based on motivational interviewing adherence sessions, including education	HIV-positive individuals (N = 20)	Self-report	RCT	Not stated	Results were positive but not statistically significant. However, participants in MI group reported being more likely to follow medication regimen as prescribed. Results show promise for the use of MI as an intervention to promote adherence to ARVs.

	Publication Details/ Country	Type of Intervention	Profile of Participants	Method Used for Measuring Adherence	Type of Study/Method for Measuring Impact	Pre- and Postintervention Levels of Adherence	Results
11	Dunbar, P. J., et al. A Two-Way Messaging System to Enhance Antiretroviral Adherence <i>Journal of American Medical Information Association</i> , 2003, 10: 11–15 USA	Reminder devices	HIV-positive individuals at clinic for underserved population (N = 25)	Self-report	Uncontrolled pilot study	Not stated	Of those still using pager after 3 months (19 of 25), 58% indicated perfect adherence over past few days, while 79% felt that the pager helped improve adherence.
12	Esch, L. D., et al. <i>Intensive Adherence Interventions to Improve Virologic Response to Antiretroviral Therapy in Treatment Naive Patients</i> 8th Conference on Retroviruses and Opportunistic Infections, 2002, Chicago, IL [Abstract 481] USA	Reminder devices, intensive coaching, dedicated phone line, and education	HIV-positive individuals who were ART-naïve (N = 60)	Self-report and viral load	Prospective, case- controlled study	Not stated	Tailored ART and intensive adherence interventions during the first 16 weeks of therapy are associated with increased self- reported adherence and enhanced virologic response.

	Publication Details/ Country	Type of Intervention	Profile of Participants	Method Used for Measuring Adherence	Type of Study/Method for Measuring Impact	Pre- and Postintervention Levels of Adherence	Results
13	Fairley, C. K., et al. Randomized Trial of an Adherence Program for Clients with HIV <i>International Journal on STDs AIDS</i> , 2003, 14(12): 805–9 Australia	Education, individualized planning of regimens, and use of adherence aids/reminder devices	HIV-positive adults (N = 43)	Self-report	Randomized step wedge design	Not stated	The adherence package improved self-reported adherence during the last 4–7 days but not for the last 28 days.
14	Fischl, M., et al. <i>Impact of Directly Observed Therapy on Long-term Outcomes in HIV Clinical Trials</i> 7th Conference on Retroviruses and Opportunistic Infections, 2000, San Francisco, CA [Abstract 71] USA	DOT	HIV-positive treatment- naïve individuals in a prison setting (captive population) (N = 100)	HIV RNA levels	Comparative group study	Not stated	Subjects in the DOT group had greater short- and long-term virologic responses.

	Publication Details/ Country	Type of Intervention	Profile of Participants	Method Used for Measuring Adherence	Type of Study/Method for Measuring Impact	Pre- and Postintervention Levels of Adherence	Results
15	Gifford, A. L., et al. <i>Effects of Group HIV Patient Education on Adherence to ARVs: A Randomized Controlled Trial</i> 8th Conference on Retroviruses and Opportunistic Infections, 2002, Chicago, IL [Abstract 479] USA	Group patient education and social support vs. social support alone vs. receipt of printed materials	HIV-positive individuals (N = 168)	Self-report	Prospective RCT	Where baseline adherence level was 100%, postintervention was 85%; where baseline adherence was 80–99%, postintervention was 47%; and where baseline was <80%, postintervention level was 13%	Group patient education and support program using a self-management approach can significantly improve adherence; however, improvements may not persist over time.
16	Goujard, C., et al. Impact of a Patient Education Program on Adherence to HIV Medication: A Randomized Clinical Trial <i>Journal of Acquired Immune Deficiency Syndromes (JAIDS)</i> , 2003, 34(2):191–94 France	Education session accompanied by reminder device	HIV-positive individuals (N = 326)	Self-report, CD4+, and HIV RNA levels	Prospective RCT	Not stated	The educational intervention affected adherence and knowledge in the experimental group at 6 months, which was maintained at 12 and 18 months; however, increased reported adherence did not result in any significant impact on CD4+ cell count and viral load.

	Publication Details/ Country	Type of Intervention	Profile of Participants	Method Used for Measuring Adherence	Type of Study/Method for Measuring Impact	Pre- and Postintervention Levels of Adherence	Results
17	Hirschhorn, L. R., et al. <i>Longer Term Impact of a Short Term Adherence Intervention for Highly Active Antiretroviral Therapy (HAART)</i> XV International AIDS Conference, 2004, Bangkok [Abstract WePeB5832] USA	Social support and counseling through home nurse visits and a multidisciplinary adherence program at the start of HAART	HIV-positive individuals (N = 50)	Self-report, HIV RNA levels and CD4+ counts	RCT	3 months after the intervention adherence level was 78%; 12 months after the intervention it was 79%	Early home nurse visits have a significant impact on HIV RNA levels at month 3 and in patients' confidence to take HAART properly. Larger trials are needed to assess long-term impact.
18	Jones, D. L., et al. Influencing Medication Adherence among Women with AIDS <i>AIDS Care</i> , 2003, 15(4):463–74, USA	Cognitive- behavioral stress management expressive supportive therapy intervention	HIV-positive women (N = 174)	Self-report	RCT	Baseline adherence level was 68% (study chose 80% as the optimum level of adherence); 52% of the women in the study reported adherence of $\geq 80\%$. Average reported adherence among women who responded poorly was 48%.	The intervention, which was not designed to influence adherence, in fact did not improve adherence.

	Publication Details/ Country	Type of Intervention	Profile of Participants	Method Used for Measuring Adherence	Type of Study/Method for Measuring Impact	Pre- and Postintervention Levels of Adherence	Results
19	Khanlou, H., et al. Pilot Study of Directly Observed Therapy in Highly Nonadherent HIV-Infected Patients in an Urban Community- Based Institution <i>JAIDS</i> , 2003, 33(5):651–52 USA	DOT following educational and adherence classes	Highly nonadherent HIV-positive individuals (N = 14)	HIV viral load and CD4+ counts	Pre-post cohort analysis?	Not stated	Results suggest that 6-week outpatient- based DOT aimed at improving adherence to HAART leads to a decline in viral load up to 24 weeks.
20	Kibangou, N. <i>A Therapeutic Advisor for Adherence to HAART in C.T.A, Pointe-Noire, Congo</i> XV International AIDS Conference, 2004, Bangkok [Abstract WePeB5797] Congo	Therapeutic adviser providing social support and counseling based on an assessment of the patient's individual needs	HIV-positive individuals (N = 49)	Pill count, CD4+ levels		Not stated	Adherence seems to have improved from 77% in month 1 to 91% in month 6.

	Publication Details/ Country	Type of Intervention	Profile of Participants	Method Used for Measuring Adherence	Type of Study/Method for Measuring Impact	Pre- and Postintervention Levels of Adherence	Results
21	Knobel, H., et al. Adherencia al Tratamiento Antirretroviral de Gran Actividad: Impacto de una Intervención de Asesoramiento Individualizado <i>Enfermedades Infecciosas y Microbiología Clínica</i> , 1999, 17:78–81 Spain	Individual counseling (in person and over telephone)	HIV-positive individuals (N = 170)	Self-report and pill counts	Randomized open trial	Not stated	Individualized counseling sessions improved adherence.
22	Kongsawat, S., et al. <i>People Living with HIV/AIDS, a Living Tool for Adherence</i> XV International AIDS Conference, Bangkok, 2004 [Abstract MoOrD1025] Thailand	Counseling and social support	HIV-positive children and their caregivers	Unclear		Not stated	The involvement of PLWHA in treatment support programs may enhance adherence to ART among children.

	Publication Details/ Country	Type of Intervention	Profile of Participants	Method Used for Measuring Adherence	Type of Study/Method for Measuring Impact	Pre- and Postintervention Levels of Adherence	Results
23	Lyon, M. E., et al. A Family Group Approach to Increasing Adherence to Therapy in HIV-Infected Youths: Results of a Pilot Project <i>AIDS Patient Care and STDs</i> , 2003, 17(6):299– 308 USA	Social support (combined family group and peer approach) and reminder devices	HIV-positive adolescents and family members (N = 23 of each)	Self-report	Longitudinal	Not stated	Inclusion of family members and peers as part of a support network is one effective strategy for improving adherence.
24	Mannheimer, S., et al. <i>Sustained Benefit from a Long-Term Antiretroviral (AR) Adherence Intervention: Results of a Large Randomized Clinical Trial</i> XV International AIDS Conference, 2004, Bangkok [Abstract LbOrB15] USA	Individualized social support using standardized assessment instruments vs. reminder devices (medication alarm)	ART-naïve HIV-positive individuals (N = 928)	Self-report, HIV RNA levels and CD4+ counts	RCT	Not stated	Social support patients were significantly more likely to have low HIV RNA levels, a greater CD4+ increase, and a higher proportion reporting 100% adherence. No benefit was seen with the reminder device.

	Publication Details/ Country	Type of Intervention	Profile of Participants	Method Used for Measuring Adherence	Type of Study/Method for Measuring Impact	Pre- and Postintervention Levels of Adherence	Results
25	Mitty, J. A., et al. Directly Observed Therapy (DOT) for the Treatment of People with Human Immunodeficiency Virus Infection: A Work in Progress <i>Clinical Infectious Diseases</i> , 2002, 34(7):984–90 USA	M-DOT	HIV-positive patients who were willing but unable to successfully administer medication through a clinic-based program (N = 44)	HIV RNA levels	Uncontrolled pilot study	Not stated	At 12–16 weeks, participants remaining in the study had lower HIV RNA levels than prior to the study.
26	Molassiotis, A., et al. A Pilot Study of the Effects of a Behavioral Intervention on Treatment Adherence in HIV-Infected Patients <i>AIDS Care</i> , 2003, 15(1):121–35 Hong Kong	Behavior change: individualized education and counseling, follow- up calls, and positive reinforcement and encouragement	HIV-infected nonadherent men (N = 6)	Self-report	Prospective cohort study	Baseline adherence was 80.27%; adherence immediately after intervention was 92.12%; after 1 month: 91.32%; after 3 months: 92.55%; 3 months postintervention: 97.5%	Initial assessment of the study suggested intervention enhanced adherence.

	Publication Details/ Country	Type of Intervention	Profile of Participants	Method Used for Measuring Adherence	Type of Study/Method for Measuring Impact	Pre- and Postintervention Levels of Adherence	Results
27	Murphy, D. A., et al. Results of a Pilot Intervention Trial to Improve Antiretroviral Adherence among HIV- Positive Patients <i>Journal of the Association of Nurses in AIDS Care</i> , 2002, 13(6):57–69 USA	Multicomponent (behavioral strategies, patient information, and social support) and multidisciplinary (cognitive- behavioral therapy and nursing) medication adherence intervention	HIV-positive individuals (N = 33)	Self-report	RCT	Not stated	The study did not significantly improve adherence to HIV medications.
28	Ncama, B. P., et al. <i>Social Support and Medication Adherence in HIV Disease in South Africa</i> XV International AIDS Conference, 2004, Bangkok [Abstract WePeB5769] South Africa	Social support	HIV-positive individuals (N = 149)	Self-report	Cross- sectional descriptive design	Not stated	There were no significant relationships between measures of social support and measures of adherence.

	Publication Details/ Country	Type of Intervention	Profile of Participants	Method Used for Measuring Adherence	Type of Study/Method for Measuring Impact	Pre- and Postintervention Levels of Adherence	Results
29	Muko, K. N., et al. <i>Compliance to Antiretrovirals: The Impact of Adherence Enhancers on Patients</i> ICIUM, 2004, Chiang Mai, Thailand [Abstract HI004] Cameroon	Adherence enhancers, including provision of free drugs for OIs, free laboratory monitoring (except CD4+), VCT for relations of victims, and active involvement of at least two relatives in care management	HIV-positive patients with CD4+ counts <600 (N = 186)	Self-report	Cohort controlled study	Not stated	Adherence was significantly higher for study group patients than for control group. Patients perceived that involvement of relatives in management and provision of free VCT to relatives had greater impact on adherence than provision of free drugs for OIs and free laboratory investigations.
30	Nykyforchyn, M. B., et al. <i>Using Directly Delivered Therapy (DDT) to Improve ART Adherence among Urban Indigent Women</i> XV International AIDS Conference, 2004, Bangkok [Abstract WePeB5812] USA	DDT using outreach workers	HIV-positive urban indigent women (N = 26)	Self-report and pill count	Pre-post cohort study	Not stated	Direct delivery of medications using a community-based liaison may be an important strategy for adherence among those initiating their first ART regimen and may be an important tool globally as access to ART increases.

	Publication Details/ Country	Type of Intervention	Profile of Participants	Method Used for Measuring Adherence	Type of Study/Method for Measuring Impact	Pre- and Postintervention Levels of Adherence	Results
31	Pradier, C., et al. Efficacy of an Educational and Counseling Intervention on Adherence to Highly Active Antiretroviral Therapy: French Prospective Controlled Study <i>HIV Clinical Trials</i> , 2003, 4(2):121–31 France	Education and counseling	HIV-positive individuals (N = 244)	Self-report and HIV RNA levels	Prospective RCT	Not stated	The educational and counseling intervention was efficient for increasing adherence to HAART.
32	Ranta, V., et al. <i>The Effect of Peer Counseling on Adherence in Women in a Managed Care Setting</i> XV International AIDS Conference, 2004, Bangkok [Abstract B12512] USA	Female peer counseling	HIV-positive women on HAART (N = 59)	Self-report	Pre-post cohort study	Not stated	Doctor reported adherence increased 40% for 58%. Patient reported adherence went from 28% to 65.6%.

	Publication Details/ Country	Type of Intervention	Profile of Participants	Method Used for Measuring Adherence	Type of Study/Method for Measuring Impact	Pre- and Postintervention Levels of Adherence	Results
33	Rigsby Michael O et al. Cue-Dose Training with Monetary Reinforcement: Pilot Study of an Antiretroviral Adherence Intervention <i>Journal of General Internal Medicine</i> , 2000, 15(12):891–3 USA	Personalized cues for remembering dose times and MEMS feedback vs. personalized cues with cash reinforcement for correctly timed bottle opening vs. control group	HIV-positive individuals on stable ART regimens (N = 55)	MEMS	Randomized trial	Authors mention that baseline adherence level was 69%, but does not state actual figures for the increase in adherence levels	Cue-dose training with cash reinforcement led to transient improvement in adherence to ART; however, no sustained improvement beyond the active training period was detected.
34	Roca, B., et al. <i>Usefulness of an Education Program to Improve Adherence and Efficacy of Anti-HIV Therapy</i> XV International AIDS Conference, 2004, Bangkok [Abstract TuPeE5357] Spain	Education: audiovisual and workbook; motivational interviewing; self-management promoting patient involvement	HIV-positive individuals (N = 144)	Self-report, HIV RNA levels and CD4+ counts	Pre-post cohort. No control	Self-reported adherence from patients (N = 119): 83%. Patients with >90% preintervention and 3 months postintervention (N = 108): 75%; (N = 101): 86%	Adherence increased following the education program, as did CD4+ counts. HIV RNA levels decreased.

	Publication Details/ Country	Type of Intervention	Profile of Participants	Method Used for Measuring Adherence	Type of Study/Method for Measuring Impact	Pre- and Postintervention Levels of Adherence	Results
35	Safren, S. A., et al. Use of an On-Line Pager System to Increase Adherence to Antiretroviral Medications <i>AIDS Care</i> , 2003, 15(6):787–93 USA	Reminder system using pagers and Web-based technology	HIV-positive individuals with a short history (2 weeks) of less than 90% adherence (N = 82)	MEMS	RCT	Baseline (among intervention group): 55%; 2 weeks postintervention: 70%; 12 weeks postintervention: 64%	Although improvement in adherence levels resulted from the intervention, improvement was minimal and adherence in both groups was still poor. More-intensive interventions may therefore be required for patients with preexisting adherence problems.
36	Safren, S. A., et al. Two Strategies to Increase Adherence to HIV Antiretroviral Medication: Life-Steps and Medication Monitoring <i>Behaviour Research and Therapy</i> , 2001, 39(10):1151–62 USA	Comparison of two interventions: (1) “Life-steps” (single- session intervention using cognitive- behavioral, motivational interviewing, and problem-solving techniques) vs. (2) self-monitoring using a pill diary and adherence questionnaire	HIV-positive individuals who self- reported less than perfect adherence (N = 56)	Self-report	Uncontrolled pilot study	Not stated	Both interventions yielded improvement in adherence from baseline; the “Life- steps” interventions showed faster improvements in adherence.

	Publication Details/ Country	Type of Intervention	Profile of Participants	Method Used for Measuring Adherence	Type of Study/Method for Measuring Impact	Pre- and Postintervention Levels of Adherence	Results
37	Samet, J. H., et al. <i>A Randomized Controlled Trial of a Multidimensional Intervention to Enhance Adherence to Antiretroviral Therapy in HIV-Infected Patients with a History of Alcohol Problems</i> XIV International AIDS Conference, 2002, Barcelona [Abstract MoPeB3286] USA	Motivational interviewing and use of reminder devices	HIV-positive individuals with a history of alcohol problems (N = 151)	Self-report and electronic monitoring, CD4+ count and HIV RNA load	RCT	Not stated	Specific, repeated, and multidimensional interventions to enhance adherence among HIV-infected persons with a history of alcohol problems did not change medication adherence.
38	Siripong, A., et al. <i>Improving Adherence to ARV in Thai Children Using Low-cost Tools Focusing on Positive Reinforcement</i> XV International AIDS Conference, 2004, Bangkok [Abstract WePeB5779] Thailand	Social support: pill boxes, stickers, and weekly diaries (designed into a game)	Caregivers of HIV-positive children who have failed a past regimen ("N =" not stated)	Diaries used to assess adherence (proxy for self- report)	Pre-post no control	Not stated	Positive reinforcement, low-cost interventions may help increase adherence among HIV-positive children.

	Publication Details/ Country	Type of Intervention	Profile of Participants	Method Used for Measuring Adherence	Type of Study/Method for Measuring Impact	Pre- and Postintervention Levels of Adherence	Results
39	Smith, S. R., et al. A Medication Self- Management Program to Improve Adherence to HIV Therapy Regimens <i>Patient Education and Counseling</i> , 2003, 50:187–99 USA	Self-management intervention based on feedback of adherence performance and principles of social cognitive theory	HIV-positive individuals (N = 43) who were starting or switching to a new protease inhibitor	MEMS	RCT	Not stated	Individuals in the intervention group were significantly more likely to take 80% or more of their doses each week than individuals in the control group.
40	Stenzel, M. S., et al. Enhancing Adherence to HAART: A Pilot Program of Modified DOT <i>The AIDS Reader</i> , 2001, 11(6): 317–28 USA	DOT: modified with special emphasis on social support	HIV-positive individuals with a history of poor adherence (N = 37)	Self-report (for nonobserved doses) and HIV RNA levels	Uncontrolled pilot	Not stated	Self-reported adherence to nonobserved doses improved and those who remained in the program for a year (N = 18) demonstrated a decrease from baseline in plasma HIV RNA levels.

	Publication Details/ Country	Type of Intervention	Profile of Participants	Method Used for Measuring Adherence	Type of Study/Method for Measuring Impact	Pre- and Postintervention Levels of Adherence	Results
41	Stephenson, B., et al. <i>Directly Observed Therapy (DOT) Does Not Ensure Adherence to Antiretroviral Therapy Among HIV-Infected Inmates</i> American Public Health Association (APHA) Conference, 2000, [Abstract 13143] USA	DOT	HIV-positive individuals in a prison setting (captive population) (N = 11)	Electronic Drug Monitoring Devices (eDEM) vs. medication administration records	N/A	Patients receiving the intervention DOT with medication administration records: 92%; those who received DOT with electronic drug monitoring devices: 71%; those who had a keep-on person with an electronic drug monitoring device: 68%	DOT did not appear to enhance adherence above self- administered medications.
42	Tuldrà, A., et al. Prospective Randomized Two-Arm Controlled Study to Determine the Efficacy of a Specific Intervention to Improve Long-Term Adherence to Highly- Active Antiretroviral Therapy <i>JAIDS</i> , 2000, 25: 221– 28 Spain	Ongoing psycho- educative intervention based on self-efficacy theory	HIV-positive individuals starting their first- or second-line HAART (N = 116)	Self-report and HIV RNA levels	RCT	After 48 weeks of the intervention the patients in the intervention group had an adherence level of 94%	Patients in the intervention group maintained high levels of adherence, while patients in the control group reverted to lower levels of adherence.

	Publication Details/ Country	Type of Intervention	Profile of Participants	Method Used for Measuring Adherence	Type of Study/Method for Measuring Impact	Pre- and Postintervention Levels of Adherence	Results
43	<p>Wall, T. L., et al. Adherence to Zidovudine (AZT) among HIV-Infected Methadone Patients: A Pilot Study of Supervised Therapy and Dispensing Compared to Usual Care</p> <p><i>Drug and Alcohol Dependence</i>, 1995, 37(3):261–69</p> <p>USA</p>	Supervised therapy and dispensing (DOT) using MEMS	HIV-positive methadone maintenance patient who demonstrated problems adhering to AZT (captive population) (N = 27)	Self-report, erythrocyte mean corpuscular volume (MCV), MEMS, and pill counts	RCT	Not stated	Supervised therapy and dispensing may be an effective strategy for improving AZT adherence, but only while provided.

ANNEX 3. REFERENCES

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